Combined preparation of anti-infectiously active compounds which inhibit the 2-C-methylerythrose-4 metabolic pathway, and inhibitors of lipid metabolism

The invention relates to combined preparations of anti-infectiously active compounds which inhibit the 2-C-methylerythrose-4 metabolic pathway as well as their salts and esters and of inhibitors of lipid metabolism and their simultaneous, separate or successive use in prophylactics and therapy of infectious processes in plants, humans, and animals as well as their use as herbicides. The lipid metabolism inhibitors according to the present invention suit in particular for the therapeutic and prophylactic treatment of infections by unicellular or multicellular parasites, fungi, bacteria or viruses as well as as herbicides.

The suitability of different organophosphoric compounds as well as of some of their esters and salts as pharmaceutical compositions is already known.

For example the antimicrobial efficacy of aminohydrocarbyl phosphonic acid derivatives against bacteria in humans and animals and against fungi in plants has been described (DE 27 33 658 A1, US 4,143,135, US 4,182,758 and US 4,206,156, US 4,994,447, US 4,888,330, US 4,210,635, US 3,955,958, US 4,196,193, US 4,268,503, US 4,330,529, US 5,189,030, US 3,764,677, US 3,764,676). Further substances of these groups have been described as herbicides (US 4,693,742, US 5,002,602, US 4,131,448, US 3,977,860, US 4,062,669), as algicides (US 3,887,353), as plant growth regulators (US 4,127,401, US 4,120,688, US 3,961,934, US 4,431,438, US 3,853,530, US 4,205,977, US 4,025,332, US 3,894,861) and as reagents in the production of pigments (US 4,051,175).

The application for example of aminohydrocarbyl phosphonic acid derivatives in the control of bacterial infections proved to be very difficult. Many bacteria which are responsible for ambulant infections and for infections which have been caught during a clinical stay are not sensitive to therapy by this group. Bacteria of the genus Staphylococcus belong to them, in particular the species Staphylococcus aureus. This germ of skin is a danger for the patient who stay in a clinic. Further studies including a phase IIa study of the applicant of the patent application DE 27 33 658 show a very quick built-up of resistance of the originally sensitive germs. Therefore these derivatives have not established in clinical application.

Further, also the use of bisphosphonic acids and some of their derivatives in pharmaceutical compositions is already known. Up to now, the microbiostatic efficacy of bisphosphonic acids (DE 3 611 522), their efficacy in the treatment of disorders in the calcium and phosphate metabolic pathway (DE 2 534 390, DE 2 534 391, DE 3 334 211, DE 3 434 667, DE 2 745 083), the cytostatic efficacy (DE 3 425 812), their lipid lowering efficacy (Arzneimittelfor-

schung 46, 759-62) and their capacity for stimulating immuncompetent cells (WO 97/38 696) is known.

The antimicrobial efficacy of fosfonochlorine against bacteria and an effect of foscarnet against viruses have been described. Further, the suitability of fosamine ammonium and N,N-dimethyl-(hydroxy-2-oxo-2-methoxyethyl) phosphonoamide as herbicides have been reported.

The use of inhibitors of the lipid metabolism is a for a longer time past accepted and widespread principle of treatment. These inhibitors are used for reducing the risk of heart and vascular diseases caused by hyperlipidaemia. The pharmacotherapy of said hyperlipidaemia in general is based on regulating the intake and controlling the synthesis of fats or in particular of cholesterol. Generally the synthesis of cholesterol is controlled by enzyme β-hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase). In general the self synthesis of cholesterol is higher than the intake by food. (Berthold H.K., of Bergmann K., Dtsch. Med. Wochenschr.121, S.729 (1996); Richter W.O., Fortschr. med. 114, S. 177, 193)

Anion exchangers and β-sitosterol are known for controlling the intake of fats from the digestive tract. The ion exchangers contain cholestyr amine and colestipol. They resorb bile acids and thereby interrupt the entero hepatic return transportation and thereby cause a significant increase of sterolene in faeces. β-Sitosterol is a phytogenic sterol structurally related to cholesterol. It inhibits the resorption of food cholesterol at the intestinmucosa.

Further, nicotinic acids and their derivatives, clofibrate and their derivatives and probucol have been used for controlling the lipid metabolism or the prevention of subsequent diseases of hyperlipidaemia. Nicotinic acids and nicotinic acid derivatives lead to a lowering of fatty acids, triglyceride and cholesterol. Up to now the mechanism is not known. The ethyl ester of clofibrin acid, clofibrate and derivatives as well as analogues lead to a lowering of cholesterol, the mechanism of action is also not known. Also the mechanism of action of probucol is not clarified.

For controlling the synthesis HMG-CoA synthetase inhibitors (US 50 64 856, US 47 51 237), HMG-CoA reductase inhibitors (US 38 18 080, US 39 83 140, US 40 49 495, US 41 37 322, US 42 55 444, US 41 98 425, US 42 62 013, US 42 31 938, US 43 75 475, US 43 46 227,US 44 106 29, US 44 447 84, US 44 50 171, US 45 54 359, US 49 201 09, EP 0065835A1, EP 0142146A2, GB 15 86 152, US 33 75 475, GB 21 62 179A, EP 164698A, WO 8402903, WO 8401231, WO 8603488A US 46 81 893, US 46 45 858, US 52 36 946, US 55 06 262, US 50 25 017, US 48 47 271, US 46 22 338, US 49 04 646, US 48 73 345, US 55 93 971, US 52 60 305, US 52 02 327, US 49 40 727, US 52 72 166, US 53 85 932, US 54 61 039, US 55 56

990, US 55 61 143, US 55 63 128), inhibitors of squalene synthetase, in particular pyrophosphates, pyrophosphate derivatives, bisphosphonic acid derivatives, phosphinylmethylphosphonic acid derivatives, phosphinylformyl derivatives, phosphonocarboxyl derivatives, phosphonosulfonic acid derivatives, phosphinylmethylphosphonic acid derivatives, which partly are known as pharmaceutical and cosmetic preparations for controlling the calcium and phosphate metabolism (DE 25 34 390, DE 25 34 391, DE 33 34 211, DE 34 34 667, DE 27 45 083, US 53 12 814, US 52 54 544, US 54 70 845, US 50 25 003, US 55 34 532, US 48 71 721, WO 92 15 579, US 51 35 935, WO 92 12 160, WO 92 12 159, WO 92 12 158, WO 92 12 157, WO 92 12 156, US 52 73 969, US 53 95 846, US 54 41 946, US 54 51 596, US 54 55 260, US 55 63 128, US 52 02 327, US 49 04 646), and other inhibitors of the synthesis of cholesterol (US 56 61 145, US 57 44 467) are used which assignment is not clarified. HMG-CoA reductase inhibitors competitively inhibit the rate of controlling enzyme of the synthesis of cholesterol, HMG-CoA reductase. Their enzyme affinity is up to 20000-times higher than that of substrate HMG-CoA. The HMG-CoA reductase results in transformation of HMG-CoA to mevalonate, from which besides cholesterol inter alia isopentenyl adenine as well as farnesyl pyrophosphate, the preliminary stage of dolichol and ubiquinone, originate. In bacteria, fungi and parasites which have a HMG-CoA reductase isopentenyl diphosphates are generated upon the acetate/mevalonate pathway, which is inhibited by HMG-CoA reductase inhibitors.

The first discovered inhibitors have been isolated from a penicillium (mevastatin) and an aspergillus fungi (lovastatin). The modification of the side chain led to simvastatin, the advancement of mevastatin to pravastatin. Meanwhile also a completely synthetic enzyme inhibitor (fluvastatin) is available representing a mevalonic lactone derivative of a fluorophenyl substituted indole ring.

In the past attempts for use of these substances in the control of infectious diseases have been made. In particular attempts have been made to inhibit the growth of plants, fungi, parasites, bacteria and viruses by the use of HMG-CoA inhibitors. The HMG-CoA synthetase and HMG-CoA reductase inhibitors inhibit the acetate/mevalonate pathway in some bacteria, fungi (US 50 26 554, US 50 64 856, US 49 20 111, US 49 20 113) and parasites. However many bacteria, for example Escherichia coli, do not show inhibition by HMG-CoA reductase inhibitors. Probably the reason is that these bacteria have an alternative metabolic pathway. In Escherichia coli indeed the absence of the acetate/mevalonate metabolic pathway and the presence of another metabolic pathway has been proved (Rohmer M. et al., Biochem.J. 295, S.517(1993); Lois E.M. et al., Proc. Natl. Acad. Sci. USA 95, S.2105 (1998)).

For parasites up to now no alternative metabolic pathway has been known. The applicant of the present invention succeeded in proving an alternative metabolic pathway, the so-called 1-

deoxyxylulose-5-phosphate or 2-C-methylerythrose-4-phosphate pathway for parasites. Studies of HMG-CoA-reductase inhibitors in parasites resulted in different results in dependence on the parasites. For example pathogens of schistosomiasis are not killed by high doses of lovastatin, while pathogens of malaria are killed in vitro, but not in vivo. Also the pathogens of sleeping sickness are not fully inhibited by inhibitors of HMG-CoA reductase. Similar attempts in inhibiting the increase of viruses show that cells infected by viruses loose the inhibiting influence of the HMG-CoA reductase inhibitors.

Also squalene synthetase inhibitors, such as the aminobisphosphonate, have been examined without success as inhibitors of the amoebic dysentery. A low efficiency of killing has been shown. Similar experiments with toxoplasm also show no satisfying results. Further also inhibitors of squalene monooxygenase have been developed as fungicides (US 47 82 059).

It is therefore an object of the present invention to provide agents, which may be used against infectious processes in humans, animals and plants and as herbicides and against which the built-up of resistance in plants, viruses, fungi, parasites and bacteria is significantly reduced.

Surprisingly, it has been found that the combination of anti-infectiously active compounds, which inhibit the 2-C-methylerythrose-4 metabolic pathway, and inhibitors of the lipid synthesis, in particular the synthesis of cholesterol, in particular of inhibitors of HMG-CoA reductase, and the squalene synthetase increase the scope and the effectiveness of therapy and prophylactics of infections. Surprisingly, the combination kills microorganism, which are killed neither by the first nor by the second group. Surprisingly the combinations show a significant reduction of build-up of resistance against the used compounds, which is generally the major problem in handling the compound group of lipid metabolism inhibitors.

Lipid metabolism inhibitors of anti-infectiously active compounds, which inhibit the 2-C-methylerythrose-4 metabolic pathway, and inhibitors of the lipid metabolism are suited for the therapeutic and prophylactic treatment of infections in plants, in particular in humans and animals, in particular of infections, which are caused by parasites, bacteria, fungi and viruses, and as herbicides in plants.

Lipid metabolism inhibitors according to the invention contain at least one anti-infectiously active compound, which inhibits the 2-C-methylerythrose-4 metabolic pathway and/or their esters and/or their salts. Generally, pharmaceutically acceptable salts, esters, salts of esters or compounds which upon application provide compounds according to the invention as metabolic products or decomposition products, also called "prodrugs", are included.

In the following some groups of substances are described by example which show excellent

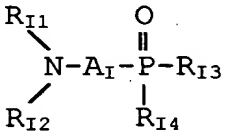
success in therapy and prophylactic treatment of infections in combination with lipid metabolism inhibitors.

The groups of anti-infectiously active substances may be determined by a method, in which the proteins being part of the 2-C-methylerythrose-4 metabolic pathway or their derivatives are contacted with the active agents to be examined, and the active agents inhibiting the proteins or derivatives are selected. The method is known by a person skilled in the art.

I. Combined preparations of lipid metabolism inhibitors and aminohydrocarbyl phosphonic acid derivatives

The aminohydrocarbyl phosphonic acid derivatives as well as their preparation have been described in DE-A1-2733658 and the PCT/EP99/02462 in detail.

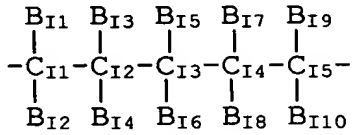
The aminohydrocarbyl phosphonic acid derivatives correspond to the general formula (I):



(I)

in which R_{I1} and R_{I2} may be the same or different and are selected from the group which consists of H, OH, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, and substituted and unsubstituted heterocyclic radicals,
R_{I3} and R_{I4} are selected from the group which consists of substituted and unsubstituted alkyl with 1 to 26 carbon atoms, substituted and unsubstituted hydroxyalkyl with 1 to 26 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl with 1 to 26 carbon atoms, substituted and unsubstituted alkynyl with 1 to 26 carbon atoms, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radicals, halogen, X_{I3} and X_{I4},
X_{I3} and X_{I4} may be the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl with 1 to 26 carbon atoms, substituted and unsubstituted hydroxyalkyl with 1 to 26 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl with 1 to 26 carbon atoms, substituted and unsubstituted alkynyl with 1 to 26 carbon atoms, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, a silyl, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids, and

A_I is an alkylene radical, alkenylene radical or hydroxy alkylene radical or corresponds to the following formula (IA):



(IA)

wherein one or more carbon atoms, selected from the group C_{I3}, C_{I4}, C_{I5}, together with their substituents may also be absent, and at least one present substitute of B_1 to B_{10} is a C_{3-8}-cycloalkyl-(C_{0-9})-alkyl group, wherein the C_{3-8}-cycloalkyl group as well as the C_{0-9}-alkyl group may comprise one or more double bonds and one or two carbon atoms of the cycloalkyl group may be replaced by nitrogen, oxygen or sulfur atoms, and wherein the cycloalkyl group as well as the alkyl group may be substituted with hydroxy, halogen, amino, oxo groups with branched or straight C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups, wherein the C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, and the remaining present substituents B_{I1} to B_{I10} are selected from the group which consists of hydrogen, hydroxy, halogen, amino groups, C_{1-26}-alkyl radicals, C_{1-26}-alkoxy radicals, C_{1-26}-alkoxy-C_{1-26}-alkyl radicals or both substituents of one C-atom together form an oxo group, wherein each C_{1-26}-alkyl radical and each C_{1-26}-alkoxy radical may be branched or straight and saturated or unsaturated with one or more double bonds and may be substituted with hydroxy, amino, halogen and oxo groups.

According to the invention the inhibitor of lipid metabolism is not an aminohydrocarbyl phosphonic acid derivative of the formula (I) if an aminohydrocarbyl phosphonic acid derivative is used as the anti-infectiously compound.

The invention also comprises the pharmaceutically acceptable salts, esters and salts of esters.

Preferably R_{I1} is OX_{I1}, R_{I3} is OX_{I3}, and R_{I4} is OX_{I4}, wherein X_{I1} is selected from the group which consists of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocyclic radical and R_{I2}, X_{I3}, X_{I4} and A_I contain the same meaning as in formula (I).

Preferably the carbon chain of A_I consists of three carbon atoms.

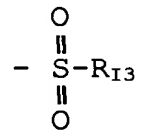
Compounds in which the carbon chain of A_I of formula (IA) consists of four carbon atoms C_{I1}, C_{I2}, C_{I3}, C_{I4} and B_{I7} or B_{I8} or both are hydroxy groups are also preferred. In this case methylene groups are also preferred for R_{I3} and R_{I4}.

Preferably B_{I1} and B_{I2} together form furthermore an oxo group. In this case the carbon chain in A_I consists of the four carbon atoms C_{I1}, C_{I2}, C_{I3}, C_{I4}.

Preferably, B_{I7} and B_{I8} together form furthermore an oxo group. In this case the carbon chain in A also consists of four carbon atoms C_{I1}, C_{I2}, C_{I3}, C_{I4}.

The carbon chain preferably consists of 5 carbon atoms C_{I1}, C_{I2}, C_{I3}, C_{I4}, C_{I5}, wherein B_{I1} and B_{I2} together form an oxo group and at least one substituent of B_{I9} or B_{I10} is a hydroxy group or B_{I9} and B_{I10} together also form an oxo group.

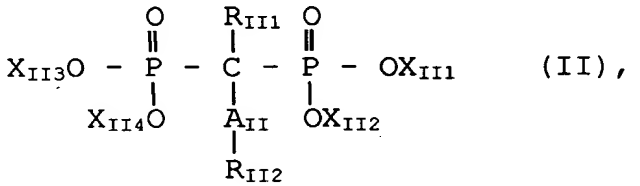
Also substances are suitable, in which a phosphonic acid or phosphinic acid or phosphinoyl group is replaced by a sulfonic group or sulfonyl group:



(IB)

II. Combined preparations of lipid metabolism inhibitor and bisphosphonic acid derivatives

The bisphosphonic acids and their derivatives are described in detail in the simultaneously filed parallel International Patent application of the same applicant.
As bisphosphonic acids and their derivatives such of the general formula



(II),

are used, wherein
X_{II1}, X_{II2}, X_{II3}, X_{II4} being the same or different are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, metals of the 1., 2. and 3. main group of the periodic systems, such as Na, K, Ca, Mg, Al as well as substituted and unsubstituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,
A_{II}, which also may be absent, is selected from the group which consists of alkylene, alkenylene and hydroxyalkylene,
R_{II1}, R_{II2}, being the same or different, are selected from the group which consists of H, OH, -

NH_2, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical and $-SR_{II3}$, Cl and $-NR_{II3}R_{II4}$, wherein

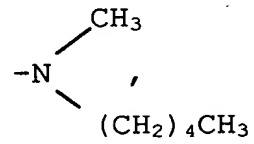
R_{II3}, R_{II4} being the same or different are selected from the group which consists of H, OH, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl and substituted and unsubstituted heterocyclic radicals, and

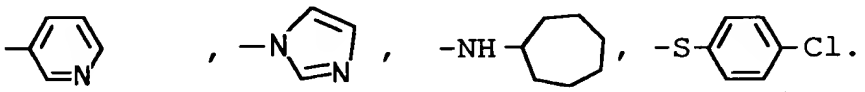
their pharmaceutically acceptable salts, esters as well as salts of esters or compounds, which upon application provide the compounds to be administered as metabolic products or decomposition products.

Bisphosphonic acid derivatives of the formula II are particularly preferred in which X_{II1}, X_{II2}, X_{II3}, X_{II4} being the same or different are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, the metals of the 1., 2., or 3. main group of the periodic systems, such as Na, K, substituted and unsubstituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,

A_{II} which also may be absent is selected from the group which consists of alkyl, $(CH_2)_{0-6}$, in particular $(CH_2)_{1-5}$ and amidino,

R_{II1} is selected from the group which consists of H, OH, NH_2, $-CH_3$, and

R_{II2} is selected from the group which consists of $-NH_2$, 



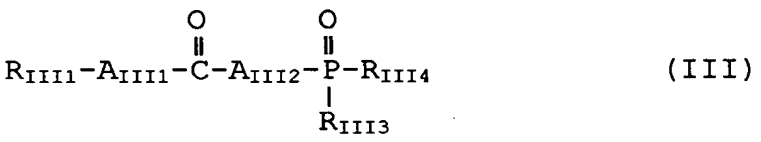
Bisphosphonates are particularly preferred, which are selected from the group which consists of amino hydroxy-methylidene-bisphosphonic acid, 2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid, 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid, amidino methylene bisphosphonic acid, 3-methylpentylamino-1-hydroxypropylidene-1,1-bisphosphonic acid, 2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid, 1-hydroxy-2-(imidazole-1-yl)-ethylidene-1,1-bisphosphonic acid, cycloheptyl aminomethylene diphosphonic acid, 4-chlorophenyl-thiomethylene-1,1-bisphosphonic acid as well as their derivatives.

If the anti-infectiously active compound is a bisphosphonic acid derivative, the lipid metabolism inhibitor is no bisphosphonic acid derivative.

III. Combined preparations of lipid metabolism inhibitor with organophosphorus compounds comprising a keto group

These compounds are described in detail in the German Patent specification DE-A-198 31 637.2.

These compounds according to the invention correspond to the general formula (III):



(III)

in which

R_{III1} is selected from the group which consists of H, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radicals, halogen and OX_{III1},

wherein X_{III1} is selected from the group which consists of hydrogen, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, a silyl, substituted and unsubstituted heterocyclic radicals, a cation of an organic and an inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds,

R_{III4} and R_{III3} may be the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical, halogen and OX_{III4} and OX_{III3},

wherein X_{III4} and X_{III3} are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, a silyl, substituted and unsubstituted heterocyclic radical, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium

compounds which derive from ethylene diamine or amino acids, and
A_{III1} and A_{III2}, of which one or both may be absent are the same or different and represent an alkylene radical, alkenylene radical, an oxo radical, a hydroxy radical or oxo hydroxyalkylene radical, wherein A_{III2} is preferably absent.

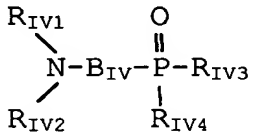
The invention comprises as well the pharmaceutically acceptable salts, amides, esters and salts of esters.

The phosphonic acid derivatives of the present invention prove to be especially suited. In this case R_{III4} is OX_{III4} and R_{III3} is OX_{III3}, wherein R_{III1}, X_{III4}, X_{III3}, A_{III1} and A_{III2} contain the same meaning as in formula (III).

Particularly preferred phosphonic acid derivatives are chloroacetyl phosphonic acid (fosfonochlorin), phosphonoformic acid (foscarnet), phosphonoacetic acid, N,N-dimethyl-(1-hydroxy-2-oxo-2-methoxy-ethyl)-phosphonamide and 2-hydroxy-2-hydroxymethyl-3-oxo-butylphosphonic acid (phosphonothrixine) and ammonium-ethylcarbamoyl phosphonate (fosamine ammonium).

IV. Combined preparations of lipid metabolism inhibitor and organophosphorus compounds which contain at least one ether group or one keto group

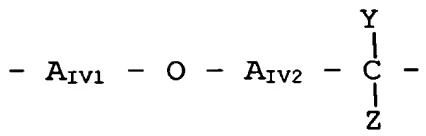
These compounds according to the invention correspond to the general formula (IV):



(IV)

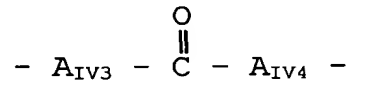
in which R_{IV1} and R_{IV2} being the same or different are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical, halogen, OX_{IV1} and OX_{IV2},
wherein X_{IV1} and X_{IV2} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radicals,

B_{IV} is selected from the group which consists of ether group (IVA)



(IVA),

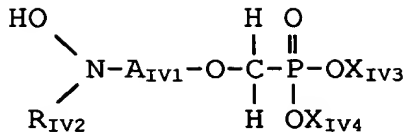
wherein A_{IV1} and A_{IV2} of which A_{IV2} also may be absent are the same or different and are selected from the group which consists of alkylene radical, alkenylene radical and hydroxyalkylene radical,
keto group (IVB)



(IVB)

wherein A_{IV3} and A_{IV4}, of which one or also both may be absent, are the same or different, are selected from the group which consists of alkylene radical, Alkenylene radical and hydroxyalkylene radical,
and 5 and 6 membered cyclic, in particular heterocyclic compounds, which contain additionally to carbon at least one heteroatom as a ring member, wherein the heteroatom is selected from the group which consists of oxygen and nitrogen,
R_{IV3} and R_{IV4} being the same or different are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl having up to 26 carbon atoms, substituted and unsubstituted hydroxyalkyl having up to 26 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl having up to 26 carbon atoms, substituted and unsubstituted alkynyl having up to 26 carbon atoms, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, halogen, OX_{IV3} or OX_{IV4},
wherein X_{IV3} or X_{IV4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl having up to 26 carbon atoms, substituted and unsubstituted hydroxyalkyl having up to 26 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl having up to 26 carbon atoms, substituted and unsubstituted alkynyl having up to 26 carbon atoms, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radicals, a silyl, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,
and their pharmaceutically acceptable salts, esters and amides and salts of esters.

In particular compounds are preferred which correspond to the formula (IVC)



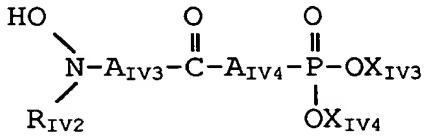
(IVC)

wherein
R_{IV2} is selected from the group which consists of acetyl and formyl,
A_{IV1} is selected from the group which consists of methylene, ethylene, ethenylene, hydroxyethylene, 2-hydroxypropylene, and
X_{IV3} and X_{IV4} are the same or different and are selected from the group which consists of sodium, potassium, methyl, ethyl.

Preferably the chain $-A_{IV1}$-O-C(ZY)- consists of one oxygen atom and two or three carbon atoms (substituents are not taken into consideration), particularly preferred two carbon atoms.

Out of the ether compounds the compounds are particularly preferred which are selected from the group which consists of ((N-formyl-N-hydroxyamino)-methoxy)-methylphosphonic acid disodium salt, ((N-acetyl-N-hydroxyamino)-methoxy)-methylphosphonic acid disodium salt, (2-(N-formyl-N-hydroxyamino)-ethenoxy)-methylphosphonic acid disodium salt, (2-(N-acetyl-N-hydroxyamino)-ethenoxy)-methyl-phosphonic acid disodium salt, (3-(N-formyl-N-hydroxyamino)-2-hydroxypropoxy)-methylphosphonic acid disodium salt, (3-(N-acetyl-N-hydroxyamino)-2-hydroxypropoxy)-methylphosphonic acid disodium salt.

Further those compounds are preferred, which correspond to the formula (IVD)



(IVD),

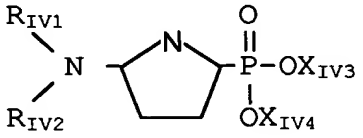
wherein R_{IV2} is selected from the group which consists of acetyl and formyl, A_{IV3} is selected from the group which consists of methylene, ethylene, ethenylene, hydroxymethylene, hydroxyethylene and 2-hydroxypropylene, A_{IV4} is absent or is methylene, and X_{IV3} and X_{IV4} are the same or different and are selected from the group which consists of a metal of the first, second or third main group of the periodic system, in particular sodium, potassium, and methyl, ethyl.

Preferably the chain $-A_{IV1}$-CO-A_{IV2}- consists of two to four carbon atoms (substituents are not taken into consideration), particularly preferred of three carbon atoms.

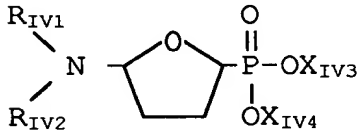
Out of these compounds 2-(N-formyl-N-hydroxyamino)-1-oxoethylphosphonic acid disodium salt, 2-(N-acetyl-N-hydroxyamino)-1-oxoethylphosphonic acid disodium salt, 3-(N-formyl-N-hydroxy amino)-1-oxopropylphosphonic acid disodium salt, 3-(N-acetyl-N-hydroxy amino)-1-oxopropylphosphonic acid disodium salt, 3-(N-formyl-N-hydroxyamino)-1-oxo-2-propenyl-phosphonic acid disodium salt, 3-(N-acetyl-N-hydroxyamino)-1-oxo-2-propenylphosphonic acid disodium salt, 4-(N-formyl-N-hydroxyamino)-1-oxo-3-hydroxybutylphosphonic acid disodium salt, 4-(N-acetyl-N-hydroxyamino)-1-oxo-3-hydroxybutyl-phosphonic acid disodium salt, 3-(N-formyl-N-hydroxyamino)-2-oxopropyl-phosphonic acid disodium salt, 3-(N-acetyl-N-hydroxyamino)-2-oxoproylphosphonic acid disodium salt, 4-(N-formyl-N-hydroxyamino)-3-oxo-2-hydroxy-2-methylbutylphosphonic acid disodium salt, 4-(N-acetyl-N-hydroxyamino)-3-oxo-2-hydroxy-2-methylpropyl-phosphonic acid disodium salt, 4-(N-formyl-N-hydroxyamino)-3-oxo-2-hydroxy-2-(hydroxymethyl)-butyl-phosphonic acid disodium salt, 4-(N-acetyl-N-hydroxyamino)-3-oxo-2-hydroxy-2-(hydroxymethyl)-propylphosphonic acid disodium salt are particularly preferred.

In the cyclic compounds the amino group and the phosphorus atom may be bound to any C-atoms of the ring. However, compounds are preferred, in which they are bound to two C-atoms, which are separated only by one additional atom. In the heterocyclic compounds both carbon atoms preferably are separated by one heteroatom.

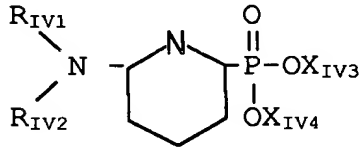
The following compounds are particularly preferred:



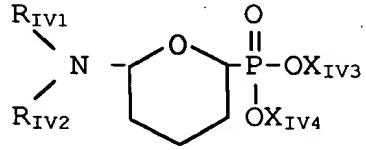
(IVE)



(IVF)

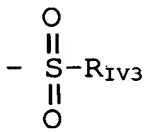


(IVG)



(IVH)

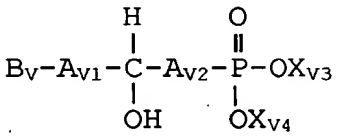
Additionally, substances are suitable in which the phosphonic acid or phosphinic acid or phosphinoyl group is replaced by a sulfonic group or sulfonyl group:



(VIIE)

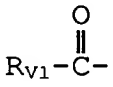
V. Combined preparations of lipid metabolism inhibitor and organophosphorus compounds which contain at least one hydroxy group

The phosphonic acid derivatives according to the invention correspond to the general formula (V):



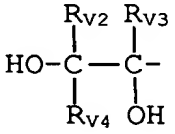
(V)

wherein A_{V1} and A_{V2}, out of which one or also both may be absent, are the same or different and are selected from the group which consists of an alkylene radical, contain an alkenylene radical and a hydroxyalkylene radical, and preferably the carbon chain $-A_{V1}$-CHOH-A_{V2}- consists of 2 to 5 carbon atoms, particularly preferred of 3-4 carbon atoms,
B_V is selected from the group which consists of a radical of formula (VA)



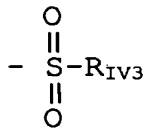
(VA)

wherein R_{V1} is selected from the group which consists of hydrogen, OH, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radicals and halogen,
of a radical of the formula (VB)



(VB)

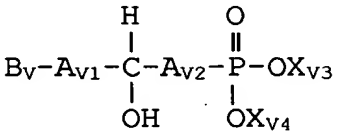
Additionally, substances are suitable in which the phosphonic acid or phosphinic acid or phosphinoyl group is replaced by a sulfonic group or sulfonyl group:



(VIIE)

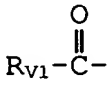
V. Combined preparations of lipid metabolism inhibitor and organophosphorus compounds which contain at least one hydroxy group

The phosphonic acid derivatives according to the invention correspond to the general formula (V):



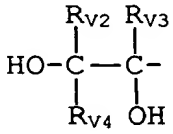
(V)

wherein A_{V1} and A_{V2}, out of which one or also both may be absent, are the same or different and are selected from the group which consists of an alkylene radical, contain an alkenylene radical and a hydroxyalkylene radical, and preferably the carbon chain $-A_{V1}$-CHOH-A_{V2}- consists of 2 to 5 carbon atoms, particularly preferred of 3-4 carbon atoms,
B_V is selected from the group which consists of a radical of formula (VA)



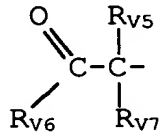
(VA)

wherein R_{V1} is selected from the group which consists of hydrogen, OH, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radicals and halogen,
of a radical of the formula (VB)



(VB)

wherein R_{V2}, R_{V3}, and R_{V4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical, halogen,
and of a radical of the formula (VC)



(VC)

wherein R_{V5}, R_{V6} and R_{V7} are the same or different and are selected from the group which consists of hydrogen, OH, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical, halogen,

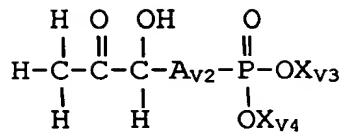
wherein X_{V3} or X_{V4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, a silyl, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,
and their pharmaceutically acceptable salts, esters and amides and salts of esters.

Preferably R_{V1} in formula (VA) is a methyl group.

Preferably in formula (VB) R_{V2} and R_{V4} are hydrogen and R_{V3} is a methyl group.

Preferably in formula (VC) R_{V5} is a methyl group, R_{V6} is selected from the group which consists of H, OH and methyl, and R_{V7} is a hydroxy group.

Particularly preferred are the compounds which correspond to the formula



(VD)

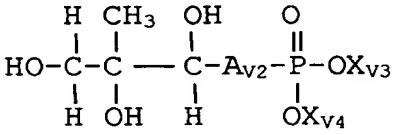
wherein

A_{V2} is a straight hydroxyalkylene with 1 to 3 carbon atoms and

X_{V3} and X_{V4} are the same or different and are selected from the group which consists of hydrogen, a metal of the first, second or third main group of the periodic system, in particular sodium, potassium, and methyl, ethyl.

Out of these compounds 3,4-dihydroxy-5-oxo-hexylphosphonic acid disodium salt, 1,2,3,4-tetrahydroxy-5-oxo-hexylphosphonic acid disodium salt, 2,3,4-trihydroxy-5-oxo-hexylphosphonic acid disodium salt, 1,2,3-trihydroxy-4-oxo-pentylphosphonic acid disodium salt and 2,3-dihydroxy-4-oxopentylphosphonic acid disodium salt are particularly preferred.

In particular additionally compounds are preferred which correspond to the formula



(VE),

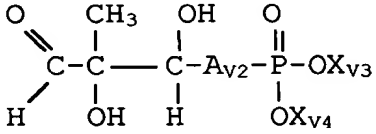
wherein

A_{V2} is a straight hydroxyalkylene with 1 to 3 carbon atoms and

X_{V3} and X_{V4} are the same or different and are selected from the group which consists of hydrogen, a metal of the first, second or third main group of the periodic system, in particular sodium, potassium, methyl and ethyl.

Out of these compounds 3,4,5-trihydroxy-4-methyl-pentylphosphonic acid disodium salt, 2,3,4,5-tetrahydroxy-4-methyl-pentylphosphonic acid disodium salt, 1,3,4,5-tetra-hydroxy-4-methylpentylphosphonic acid disodium salt, 1,2,3,4,5-pentahydroxy-4-methyl-pentylphosphonic acid disodium salt are particularly preferred.

In particular also those compounds are preferred, which correspond to the formula



(VF)

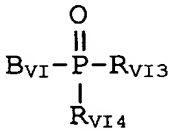
wherein A_{V2} is a straight hydroxyalkylene or a straight alkylene and consists of 1 to 3 carbon atoms and

X_{V3} and X_{V4} are the same or different and are selected from the group which consists of hydrogen, a metal of the first, second or third main group of the periodic system, in particular sodium, potassium, and methyl, ethyl.

Out of these compounds 3,4-dihydroxy-4-methyl-5-oxo-pentylphosphonic acid disodium salt, 2,3,4-trihydroxy-4-methyl-5-oxo-pentylphosphonic acid disodium salt, 1,2,3-tri-hydroxy-4-methyl-5-oxo-pentylphosphonic acid disodium salt, 2-monohydroxy-3-methyl-4-oxo-butylphosphonic acid disodium salt, 1,2-dihydroxy-3-methyl-4-oxo-butylphosphonic acid disodium salt are particularly preferred.

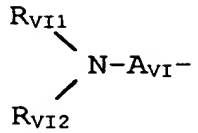
VI. Combined preparation of lipid metabolism inhibitor and organophosphorus or organosulfur compounds containing an amine or imine group

The organophosphorus compounds according to the invention correspond to the general formula (VI):



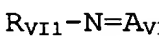
(VI)

wherein R_{VI3} and R_{VI4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl having up to 26 carbon atoms, substituted and unsubstituted hydroxyalkyl having up to 26 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl having up to 26 carbon atoms, substituted and unsubstituted alkynyl having up to 26 carbon atoms, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radicals, halogen, OX_{VI3} or OX_{VI4},
wherein X_{VI3} or X_{VI4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl having up to 26 carbon atoms, substituted and unsubstituted hydroxyalkyl having up to 26 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl having up to 26 carbon atoms, substituted and unsubstituted alkynyl having up to 26 carbon atoms, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, a silyl, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,
and B_{VI} is selected from the group which consists of the group (VIA)



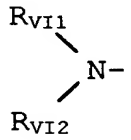
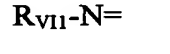
(VIA)

and the group (VIB)



(VIB),

wherein A_{VI} is selected from the group which consists of an alkyleneamine radical, an alkenyleneamine radical, a hydroxyalkyleneamine radical, an alkyleneimine radical, an alkenylene imine radical and a hydroxyalkyleneimine radical, wherein the nitrogen atom is a member of the chain which connects the phosphorus atom with the nitrogen atom of the group

 or the group  , and

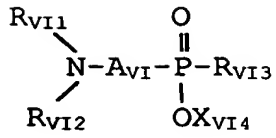
in which R_{VI1} and R_{VI2} in group (VIA) are the same or different and R_{VI1} and R_{VI2} in group (VIA) and R_{VI1} in group (VIB) are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical, halogen, OX_{VI1} and OX_{VI2},

wherein X_{VI1} and X_{VI2} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical,

and their pharmaceutically acceptable salts, esters and amides and salts of esters.

Preferably, A_{VI} is an amino group, in which the nitrogen atom is not in the end position. Preferably, A_{VI} connects the nitrogen and the phosphorus atom by three atoms (without substituents).

In particular those compounds are preferred, which correspond to the formula (VI)



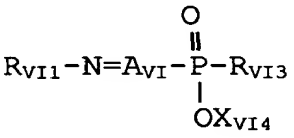
(VI)

wherein

R_{VI1}, R_{VI2}, R_{VI3} and X_{VI4} are defined the same as in formula (VI), and A_{VI} is selected from the group which consists of C-N-C, C=N-C, C-N=C, wherein the carbon atoms may be substituted with a hydroxy or alkyl group having up to 7 carbon atoms.

Particularly preferably R_{VI1} is a hydroxy group, R_{VI2} is selected from the group which consists of acetyl and formyl, R_{VI3} is selected from the group which consists of hydrogen, methyl, ethyl, hexadecyl, octadecyl and OX_{VI3}, and X_{VI3} and X_{VI4} selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl, hexadecyl and octadecyl, and may be, as far both are present, the same or different.

Further compounds are preferred which correspond to the formula (VID)



(VID)

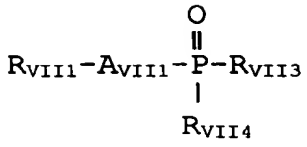
wherein

R_{VI1}, R_{VI2}, R_{VI3} and X_{VI4} are defined the same as in formula (I), and A is selected from the group which consists of C-N-C, C=N-C, C-N=C, wherein the carbon atoms may be substituted with a hydroxy or alkyl group having up to 7 carbon atom.

Particularly preferably R_{VI1} is selected from the group which consists of acetyl and formyl, and R_{VI3} is selected from the group which consists of hydrogen, methyl, ethyl, hexadecyl, octadecyl and OX_{VI3}, and X_{VI3} and X_{VI4} are selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl, hexadecyl and octadecyl, and may be the same or different as far both are present.

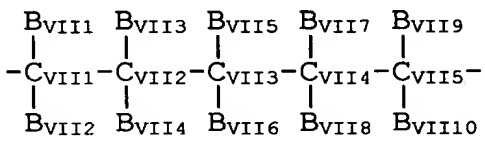
VII. Combined preparation of lipid metabolism inhibitor with organophosphorus compounds, which contain a nitrogen heterocycle

The organophosphorus compounds used according to the invention correspond to the general formula (VII):



(VII)

in which A_{VII} is selected from the group which consists of (C_{1-9})-alkylene radical, which may comprise one or more double bonds and may be substituted with hydroxy, halogen, amino, oxo groups with branched or straight C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups, wherein the C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, -C-O-C- and -C-N-C-, wherein the carbon atoms of –C-O-C- and –C-N-C- may be substituted with an alkyl having up to 7 carbon atoms or hydroxy groups, or in which A_{VII} corresponds to the following formula (VIIA):



(VIIA)

wherein one or more of the carbon atoms selected from the group C_{VII3}, C_{VII4}, C_{VII5} may also be absent together with their substituents, and at least one present substitute of B_{VII1} to B_{VII10} is a C_{3-8}-cycloalkyl-(C_{0-9})-alkyl group, wherein the C_{3-8}-cycloalkyl group as well as the C_{0-9}-alkyl group may contain one or more double bonds and one or two carbon atoms of the cycloalkyl group may be replaced by nitrogen, oxygen or sulfur atoms, and wherein the cycloalkyl group as well as the alkyl group may by substituted with hydroxy, halogen, amino, oxo groups, with branched or straight C_{1-9}-alkyl groups and with C_{2-9}-alkenyl groups, wherein the C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, and the remaining present substituents B_{VII1} to B_{VII10} are selected from the group which consists of hydrogen, hydroxy, halogen, amino groups, C_{1-26}-alkyl radicals, C_{1-26}-alkoxy radicals, C_{1-26}-alkoxy-C_{1-26}-alkyl radicals or both substituents of one C-atom together form an oxo group, wherein each C_{1-26}-alkyl radical and each C_{1-26}-alkoxy radical may be branched or straight and saturated or unsaturated with one or more double bonds and may be substituted with hydroxy, amino, halogen and oxo groups,

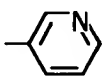
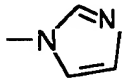
in which R_{VII1} is selected from the group which consists of 5 and 6 membered heterocycles with one or two nitrogen, oxygen or sulfur atoms in the ring, wherein the heterocycle may be saturated or unsaturated with one or more double or triple bonds and may be substituted with hydroxy, halogen, amino, oxo groups and by branched or straight C_{1-9}-alkyl groups and by C_{2-9}-alke-nyl groups, wherein the C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups may be saturated or unsaturated with one or more double or triple bonds and may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups,

in which R_{VII3} and R_{VII4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26}-alkyl, hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, halogen, OX_{VII3} and OX_{VII4},

wherein X_{VII3} and X_{VII4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26}-alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, a silyl, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,
and their pharmaceutically acceptable salts, esters and amides and salts of esters.

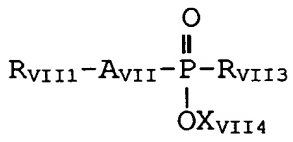
If two heteroatoms are present in the heterocycle R_{VIII}, of course they also may be present in mixed form, for example an oxygen atom and a nitrogen atom.

Preferably R_{VIII} is a heterocycle containing nitrogen atoms, wherein substituted or unsubstituted pyridine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyrrole and substituted or unsubstituted pyrazole are particularly preferred and

 or 

are especially particularly preferred.

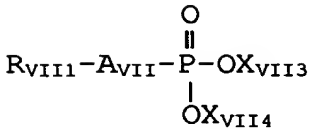
Preferably the organophosphorus compound corresponds to the formula (VIIC)



(VIIC)

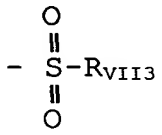
wherein R_{VII3} preferably is hydrogen, methyl, ethyl or an amide radical and X_{VII4} is selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl,

and particularly preferably correspond to the formula (VIID)



(VIID).

Additionally, substances are suitable in which the phosphonic acid or phosphinic acid or phosphinoyl group is replaced by sulfonic group or sulfonyl group:

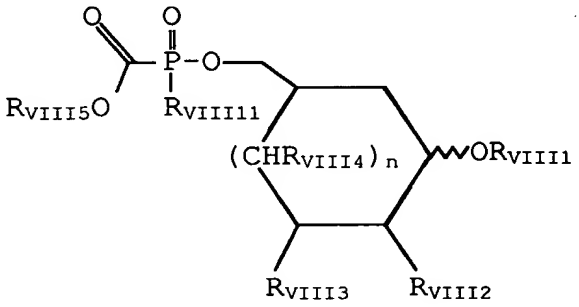


(VIIE)

VIII. Combined preparation of lipid metabolism inhibitor and phosphonoformic acid derivatives

The compounds are described in WO 98/16537.

The organophosphorus compounds used according to the present invention correspond to the general formula (VIII):



wherein the wavy line represents a bond which has either α- or β-configuration,
n is 0 or 1,
wherein R_{VIII1} is selected from the group which consists of substituted and unsubstituted C_{1-26}-alkyl, hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radicals, halogen and OX_{VIII1},
wherein X_{VIII1} is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26}-alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl,

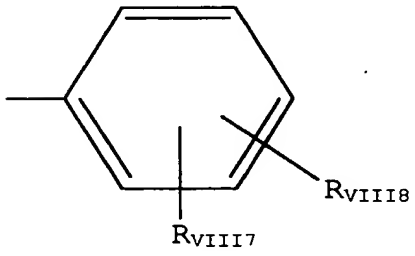
substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, a silyl, a cation of organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,

R_{VIII1} is selected from the group which consists of C_{1-24}-alkyl radicals, C_{2-24}-alkenyl radicals, C_{2-24}-alkapolyenyl radicals, which contain 2 to 6 double bonds, C_{2-24}-alkynyl radicals, C_{3-8}-cycloalkyl radicals, C_{3-8}-cycloalkyl-C_{1-24}-alkyl radicals and C_{1-12}-alkoxy-C_{1-12}-alkyl radicals,

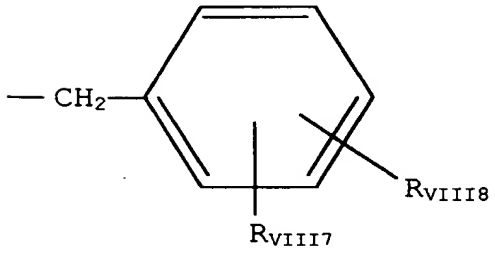
R_{VIII2}, R_{VIII3} and R_{VIII4} each are selected independently from the group which consists of hydrogen, halogen, amino, acetylamino, azido and XR_{VIII6}-groups, wherein X is O or S and R_{VIII6} is selected from the group which consists of a hydrogen radical, branched or straight C_{1-4}-alkyl radicals and C_{2-4}-alkenyl radicals, wherein the C_{1-4}-alkyl radicals as well as the C_{2-4}-alkenyl radicals optionally may be substituted with hydrogen, amino, halogen or oxo groups, or

R_{VIII2}, R_{VIII3} and R_{VIII4} together with the respective geminal hydrogen group represent an oxo group,

R_{VIII5} is selected from the group which consists of hydrogen, C_{1-24}-alkyl groups, C_{3-8}-cycloalkyl radicals, ar(C_{1-24}-alkyl) groups, aryl groups, acyl groups, heterocyclic radicals, halogen, wherein all radicals may be branched or straight and optionally may be substituted with hydroxy, amino, halogen or oxo groups and may contain 2-6 double and triple bonds or R_{VIII5} is a phenyl radical of the formula VIIIA or XIIIB,



(VIIIA)



(VIIIB)

wherein R_{VIII7} and R_{VIII8} are the same or different and are bound to any two positions of the phenyl ring and are selected independently from the group which consists of hydrogen, halo-

gen, C_{1-4}-alkyl radicals, C_{1-4}-alkoxy radicals, formyl, acetyl, propionyl, butyryl radicals, formyl, acetyl, propionyl, butyryloxy radicals, C_{2-5}-alkoxycarbonyl radicals, which all may be branched or straight, or R_7 and R_{VIII8} may form together a straight saturated alkylene chain having 3 to 4 carbon atoms bound to adjacent positions, for example the 2,3-position or 3,4-position of the phenyl ring, or R_7 and R_8 together form a methylenedioxy radical, a 1,1-ethylidenedioxy radical or a 1,2-ethylenedioxy radical, which are bound to the 2,3- or 3,4-positions of the phenyl ring, or

R_{VIII5} is selected from the group which consists of $R_{VIII9}COOCHR_{VIII10}$- and $R_{VIII9}OCOOCHR_{VIII10}$-,

wherein R_{VIII9} is selected from the group which consists of C_{1-6}-alkyl radicals, C_{2-6}-alkenyl radicals, C_{2-6}-alkynyl radicals, C_{3-8}-cycloalkyl radicals, C_{3-8}-cycloalkyl-C_{1-6}-alkyl radicals and C_{1-6}-alkoxy-C_{1-6}-alkyl radicals, wherein all radicals may be branched or straight and optionally may be substituted with hydroxy, amino, halogen or oxo groups, and

R_{10} is a branched or straight C_{1-4}-alkyl radical,

and wherein the configurations of the substituents R_{VIII2}, R_{VIII3}, R_{VIII4} and $R_{VIII5}OOCPO(OH)OCH_2$- in (VIII) are selected independently from D-gluco, L-gluco, D-galacto, L-galacto, D-manno, L-manno, D-talo, L-talo, D-allo, L-allo, D-altro, L-altro, D-gulo, L-gulo, D-ido or L-ido, if n is 1 or the configurations of the substituents R_2, R_3 and $R_5OOCPO(OH)OCH_2$- in I are independent D-ribo, L-ribo, D-arabino, L-arabino, D-xylo, L-xylo, D-lyxo or L-lyxo, if n is 0.

According to the invention the configuration of the glycosidic bond of the compounds is preferably α.

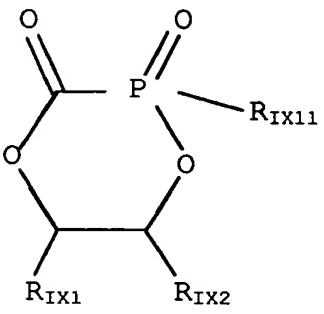
Preferred compounds of formula (VIII) are those, wherein R_{VIII1} is selected from the group which consists of C_{9-24}-alkyl radicals, C_{9-24}-alkenyl radicals, C_{9-24}-alkapolyenyl radicals, which contain 2 to 6 double bonds, C_{9-24}-alkynyl radicals, C_{3-8}-cycloalkyl-C_{6-24}-alkyl radicals and C_{1-12}-alkoxy-C_{8-12}-alkyl radicals, which each may optionally be branched or straight and may be substituted with hydrogen, amino, halogen or oxo radicals.

In particular the use of any compound is preferred, in which R_{VIII1} is selected from the group which consists of a *n*-tetradecyl radical, *n*-octadecyl-1-yl radical, a *trans*-9-octadecenyl radical and a *cis*-9-octadecen-1- radical. Preferably R_{VIII2}, R_{VIII3}, R_{VIII4} each are hydroxy groups. Preferably R_{VIII5} is a hydrogen, a formyl group or a acetyl group. Furthermore n is preferably 1 and the configuration of the substituents R_{VIII2}, R_{VIII3}, R_{VIII4}, and $R_{VIII5}OOCPO(OH)OCH_2$- is D-gluco.

Preferably R_{VIII11} represents OX_{VIII11} with X_{VIII11} = hydrogen.

IX. Combined preparation of lipid metabolism inhibitor and heterocyclic phosphonoformic acid derivatives

The organophosphorus compounds according to the invention are described in WO98/16537 and correspond to the formula (IX)



(IX)

wherein R_{IX11} is selected from the group which consists of substituted and unsubstituted C_{1-26}-alkyl, hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, halogen and OX_{IX11},
wherein X_{IX11} is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26}-alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, a silyl, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,
wherein R_{IX1} and R_{IX2} each are selected independently from the group which consists of C_{1-24}-alkyl radicals, C_{3-8}-cycloalkyl radicals, C_{3-8}-cycloalkyl-C_{1-24}-alkyl radicals, C_{1-24}-alkoxy radicals, C_{1-24}-alkylthio radicals, C_{1-24}-alkoxy-C_{1-24}-alkyl radicals and C_{1-24}-alkylthio-C_{1-24}-alkyl radicals, acyl radicals, aryl radicals, aralkyl radicals, heterocyclic radicals, halogen and hydrogen, and each C_{1-24}-alkyl radical and C_{1-24}-alkoxy radical may be branched or straight and may be saturated or unsaturated with 2 to 6 double bonds and optionally may be substituted with hydroxy, amino, mercapto, halogen, oxo groups or C_{1-24}-alkoxy radicals, C_{1-24}-alkylcarbonyl-oxy radicals, C_{1-24}-alkoxycarbonyloxy radicals, C_{1-24}-alkylthio radicals, C_{1-24}-alkylcarbonyl-thio radicals, C_{1-24}-alkylamino radicals, di-(C_{1-24}-alkyl)amino radicals, C_{1-24}-alkylcabonyl-amino radicals, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino radicals, C_{1-24}-alkoxycarbonylamino radicalsorC_{1-24}-alkyl-(C_{1-24}-alkoxycarbonyl)amino radicals, wherein each aralkyl radical, heterocyclic radical, C_{1-24}-alkyl radical and C_{1-24}-alkoxy radical may be

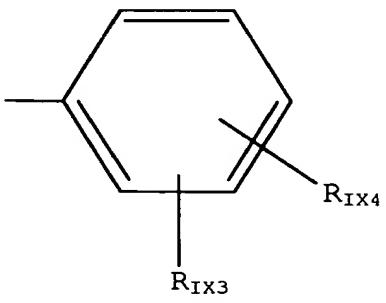
branched or straight and may be saturated or unsaturated with 2 to 6 double bonds or triple bonds, or

wherein R_{IX1}-CH-CH-R_{IX2} form part of a C_{4-8}-carbon ring, which optionally may be substituted with hydroxy, mercapto, amino, halogen, oxo groups or with C_{1-24}-alkyl radicals, C_{1-24}-alkoxy radicals, C_{1-24}-alkylthio radicals, C_{1-24}-alkylamino radicals, di-(C_{1-24}-alkyl)amino-radicals, C_{1-24}-alkylcabonyl radicals, C_{1-24}-alkylcarbonyloxy radicals, C_{1-24}-alkoxycarbonyl radicals, C_{1-24}-alkylcarbonylthio radicals or C_{1-24}-alkylcarbonylamino radicals, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)-amino radicals, all C_{1-24}-alkyl radical may be branched or straight and saturated or unsaturated with 1 to 6 double bonds, or

wherein R_{IX10} is a branched or straight C_{1-4}-alkyl radical, and

wherein R_{IX1}-CH-CH-R_{IX2} form a part of the furanose or pyranose ring of a sugar, for example D-ribose, D-arabinose, D-xylose, D-lyxose, D-glucose, D-galactose, D-mannose, D-talose, D-allose, D-altrose, D-gulose, D-idose or the corresponding L-isomers, wherein the hydroxy groups each may be optionally substituted with hydrogen, amino, azido, oxo, mercapto radicals or C_{1-24}-alkoxy radicals, C_{1-24}-alkylthio radicals, C_{1-24}-alkylamino radicals, di-(C_{1-24}-alkyl)amino radicals, C_{1-24}-alkylcabonyloxy radicals, C_{1-24}-alkylcarbonylthio radicals, C_{1-24}-alkylcarbonylamino radicals, C_{1-24}-alkyl-(C_{1-24}-alkylcarbonyl)amino radicals, wherein each C_{1-24}-alkyl radical may be branched or straight and saturated or unsaturated with 1 to 6 double bonds, and their pharmaceutically acceptable salts, esters and amides and salts of esters as well as their optical isomers.

In particular R_{IX1} and R_{IX2} each may be selected independently from the group which consists of carboxyl radicals, carboxamido radicals, aryl radicals, aryloxycarbonyl radicals, aryl-C_{1-24}-alkyl radicals, C_{1-24}-alkoxycarbonyloxy radicals, C_{1-24}-alkylaminocarbonyl radicals, di-(C_{1-24}-alkyl)-aminocarbonyl radicals, aryl-C_{1-24}-alkoxycarbonyl radicals, aryl-C_{1-24}-alkylamino- carbonyl radicals, C_{1-24}-alkylcabonyloxy-(C_{1-4})-alkylmethoxycarbonyl radicals, C_{1-24}-alkoxy-carbonyloxymethoxycarbonyl radicals, C_{1-24}-alkoxycarbonyl-oxy-(C_{1-4}-alkyl)-methoxycarbonyl, wherein each C_{1-24}-alkyl radical may be branched or straight and saturated or unsaturated with 2 to 6 double bonds, and each C_{1-4}-alkyl radical and C_{1-24}-alkoxy radical may be branched or straight and saturated or unsaturated, and each aryl radical corresponds to the formula IXA



(IXA)

wherein R_{IX3} and R_{IX4} are the same or different and each are selected from the group which

consists of hydrogen, halogen, C_{1-4}-alkyl radicals, C_{1-4}-alkoxy radicals, formyl, acetyl, propionyl, butyryl radicals, formyl, acetyl, propionyl, butyryloxy radicals, C_{1-4}-alkoxy carbonyl radicals, which all may be branched or straight, or R_{IX3} and R_{IX4} together form a straight saturated alkylene chain with 3 to 4 carbon atoms, which is bound to adjacent positions of the phenyl ring, or R_{IX3} and R_{IX4} together form a methylene dioxy radical, a 1,1-ethylidenedioxy radical or a 1,2-ethylenedioxy radical which is bound to adjacent positions of the phenyl ring.

The use of compounds is preferred, in which R_{IX1} and R_{IX2} each are independently selected from the group which consists of hydrogen, hydroxy groups, formyl, acetyl and methyl, wherein the methyl radical optionally may be substituted with a hydroxy group or mercapto group or with C_{1-24}-alkoxy radicals, C_{1-24}-alkylcarbonyloxy radicals, C_{1-24}-alkylthio radicals or C_{1-24}-alkylcarbonylthio radicals, wherein the C_{1-24}-alkyl groups and the C_{1-24}-alkoxy groups may be branched or straight and saturated or unsaturated with 1 to 6 double bonds.

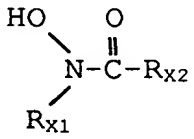
R_{IX1} is particularly preferred a methyl radical, which optionally may be substituted with a hydroxy group or mercapto group or by C_{1-24}-alkoxy radicals, C_{1-24}-alkylcarbonyloxy radicals, C_{1-24}-alkylthio radicals or C_{1-24}-alkylcarbonylthio radicals, wherein the C_{1-24}-alkyl groups and the C_{1-24}-alkoxy groups may be branched or straight and saturated or unsaturated with 1 to 6 double bonds, and R_{IX2} a hydrogen radical.

Especially good results are achieved by compounds, wherein R_{IX1} and R_{IX2} each is independently selected from the group which consists of hydrogen and a *n*-octadecylmethyl radical, wherein R_{IX1} is preferably a *n*-octadecylmethyl radical and R_2 is a hydrogen radical. Special advantages are achieved, if the compound is of configuration (R).

Preferably R_{IX11} represents OX_{IX11} with X_{IX11} = hydrogen.

X. Combined preparation of lipid metabolism inhibitor and hydroxy aminooxocarbyl derivatives

The hydroxy aminooxocarbyl derivative used according to the present invention correspond to the general formula (X):



(X)

wherein R_{X1} is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-9}-alkyl, substituted and unsubstituted hydroxy-C_{1-9}-alkyl, substituted and unsubstituted C_{1-9}-alkenyl, substituted and unsubstituted C_{1-9}-alkynyl, substituted and unsubstituted

aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical, halogen and OX_{X1},
wherein X_{X1} is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-9}-alkyl, substituted and unsubstituted hydroxy-C_{1-9}-alkyl, substituted and unsubstituted C_{1-9}-alkenyl, substituted and unsubstituted C_{1-9}-alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical,
wherein R_{X2} is selected from the group which consists of C_{1-26}-alkyl radicals, C_{1-26}-alkoxy radicals, C_{1-26}-alkoxy-C_{1-26}-alkyl- radicals, C_{3-8}-cycloalkyl-(C_{0-26})-alkyl radicals, wherein one or two carbon atoms of the cycloalkyl group may be replaced by nitrogen, oxygen or sulfur atoms, each C_{3-26}-alkyl radical and each C_{3-26}-alkoxy radical being branched or straight and each C_{3-8}-cycloalkyl radical, each C_{2-26}-alkyl radical and each C_{2-26}-alkoxy radical may be saturated or unsaturated with one or more double bonds and each C_{3-8}-cycloalkyl radical, each C_{1-26}-alkyl radical and each C_{1-26}-alkoxy radical may be substituted with hydroxy, amino, halogen and oxo groups or with the carbyl group COR_{X3},
wherein R_{X3} is selected from the group which consists of substituted and unsubstituted C_{1-26}-alkyl, hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, halogen and OX_{X3},
wherein X_{X3} is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26}-alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, a silyl, a cation of organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,.

Preferably R_{X2} represents the carboxylic acid group –COOH, wherein R_{X1} is a branched or straight C_{1-4}-alkyl group, particularly preferred an isopropyl group, as well as their pharmaceutically acceptable salts, esters and amides.

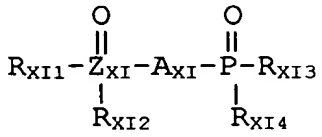
The salts of the carboxylic acid group are preferred, in which H is replaced by a metal of the first, second or third main group of the periodic system, ammonium or substituted ammonium, or ammonium compounds, which derive from ethylene diamine or amino acids. I.e. the salt compounds of hydroxy aminooxocarbylcarbonic acid derivatives and organic or inorganic bases (for example sodium salt, potassium salt, calcium salt, aluminium salt, ammonium salt,

magnesium salt, triethyl amine salt, ethanol amine salt, dicyclohexyl amine salt, ethylene diamine salt, N,N'-dibenzylethylene diamine salt etc.) as well as salts of amino acids (for example arginine salt, asparagine acid salt, glutamine acid salt etc.) and the like are formed.

Preferably additionally esters of the carboxylic acid group may be formed. Suitable examples of such esters are suitable mono and diesters, and preferred examples of such esters include alkylester (for example hexadecanylester, octadecanylester etc.).

XI. Combined preparation of lipid metabolism inhibitor and organophosphorus compounds, which either contain two oxyphosphorus groups or one oxyphosphorus group and one oxysulfur group

The organophosphorus compounds used according to the present invention correspond to the general formula (XI):



(XI)

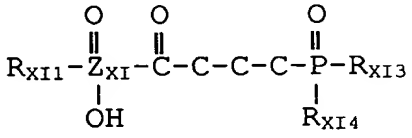
wherein Z_{XI} is a phosphorus atom or a sulfur atom,
wherein A_{XI} is a straight C_{2-9}-alkylene chain having substituents which are the same or different and are selected from the group which consists of hydrogen, hydroxy, halogen, amino and oxo groups, C_{1-26}-alkyl radicals, C_{1-26}-alkoxy radicals, C_{1-26}-alkoxy-C_{1-26}-alkyl radicalsorC_{3-8}-cycloalkyl-(C_{0-9})-alkyl radicals, wherein each C_{1-26}-alkyl radical and each C_{1-26}-alkoxy radical may be branched or straight and saturated or unsaturated with one or more double bonds and may be substituted with hydroxy, amino, halogen and oxo groups and the C_{3-8}-cycloalkyl group as well as the C_{0-9}-alkyl group of the C_{3-8}-cycloalkyl-(C_{0-9})-alkyl group may contain one or more double bonds and one or two carbon atoms of the cycloalkyl group may be replaced by nitrogen, oxygen or sulfur atoms, and wherein the cycloalkyl group as well as the alkyl group may be substituted with hydroxy, halogen, amino, oxo groups with branched or straight C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups, wherein the C_{1-9}-alkyl groups and C_{2-9}-alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, wherein R_{XI1} and R_{XI2} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-9}-alkyl, substituted and unsubstituted hydroxy-C_{1-9}-alkyl, substituted and unsubstituted C_{1-9}-alkenyl, substituted and unsubstituted C_{1-9}-alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical, halogen, OX_{XI1} and OX_{XI2}, wherein X_{XI1} and X_{XI2} are the same or different and are selected from the group which consists of hydrogen, substituted and unsub-

stituted C_{1-9}-alkyl, substituted and unsubstituted hydroxy-C_{1-9}-alkyl, substituted and unsubstituted C_{1-9}-alkenyl, substituted and unsubstituted C_{1-9}-alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic radical,
wherein R_{XI3} and R_{XI4} are the same or different and are selected from the group which consists of substituted and unsubstituted C_{1-26}-alkyl, hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, halogen, OX_{XI3} and OX_{XI4}, wherein X_{XI3} and X_{XI4} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26}-alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26}-alkenyl, substituted and unsubstituted C_{1-26}-alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic radical, silyl, cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids,
and their pharmaceutically acceptable salts, esters and amides and salts of esters.

Preferably A_{XI} is a C_{3-5}-alkyl chain.

Particularly preferred are compounds, in which R_{XI2} represents a methyl group and Z_{XI}, R_{XI1}, R_{XI3}, R_{XI4} are defined the same as above, wherein R_{XI1} is preferably substituted with a hydroxy group at the C-atom adjacent to the heteroatom,
and compounds, in which R_{XI2} represents a hydroxy group
wherein Z_{XI}, R_{XI1}, R_{XI3}, R_{XI4} is defined the same as above, wherein R_{XI1} is preferably an acyl group, particularly preferably is a formyl, acetyl, propionyl or butyryl group.

Also compounds having the following structures are preferred:



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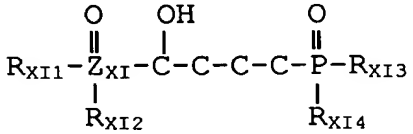

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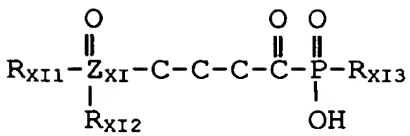
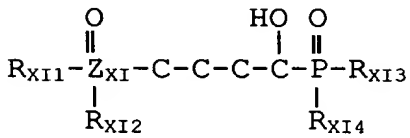
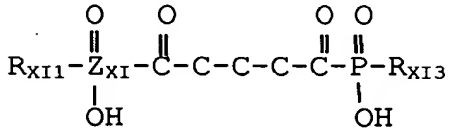


(XIC),



(XID),



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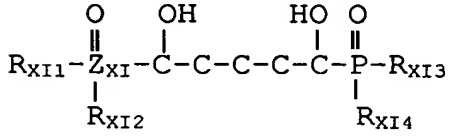

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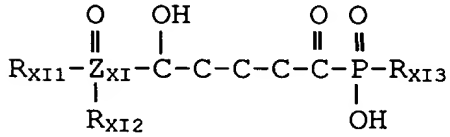
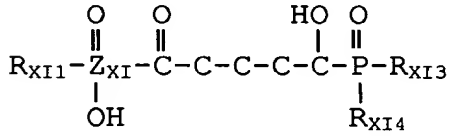


(XIG) and

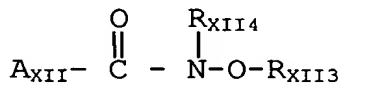


(XIH).

XII. Combined preparation of lipid metabolism inhibitor with 3-isoxazolidinones and hydroxy amine acids

These compounds are described in US patent document 4 405 357.

The compounds according to the invention contained in the pharmaceutical compositions correspond to the general formula (I):



(XII)

wherein A_{XII} is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-28}-alkyl radicals, substituted and unsubstituted alkoxy-(C_{0-28})-alkyl radicals, substituted and unsubstituted cycloalkyl-(C_{0-28})-alkyl radicals, substituted and unsubstituted cycloalkoxy-(C_{0-28})-alkyl radicals, substituted and unsubstituted amino-(C_{0-28})-alkyl radicals and substituted, unsubstituted thio-(C_{0-28})-alkyl radicals and substituted or unsubstituted acyl-(C_{0-28})-alkyl radicals and halogen, wherein each alkyl radical, each alkoxy radical and each acyl

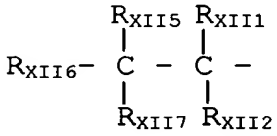
radical may be branched or straight and each alkyl radical, each alkoxy radical each acyl radical and each cycloalkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms,

R_{XII3} is selected from the group which consists of hydrogen, substituted and unsubstituted alkyl groups, substituted and unsubstituted alkoxy-(C_{0-26})-alkyl radicals, substituted and unsubstituted C_{3-14}-cycloalkyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted Cycloalkoxy-(C_{0-26})-alkyl radicals, substituted and unsubstituted amino-(C_{0-26})-alkyl radicals, substituted and unsubstituted silyl-(C_{0-26})-alkyl radicals and substituted and unsubstituted thio-(C_{0-26})-alkyl groups, wherein each alkyl radical and each alkoxy radical may be branched or straight and each alkyl radical, each alkoxy radical and each cycloalkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms,

or a carbon chain made of two C-atoms in A_{XII} forms a ring together with R_{XII3}, such that an isoxazolidone ring is formed, and

R_{XII4} is selected from the group which consists of hydrogen, substituted and unsubstituted alkyl radicals, substituted and unsubstituted acyl radicals and substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, wherein each alkyl radical and each acyl radical may be branched or straight and each alkyl radical, each acyl radical and each cycloalkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms.

Preferably A_{XII} corresponds to the formula (XIIA)



(II)

wherein R_{XII1} and R_{XII2} are the same or different and are selected from the group which consists of hydrogen, hydroxy, halogen, substituted and unsubstituted amino radicals, substituted and unsubstituted alkyl radicals, substituted and unsubstituted alkoxy radicals and substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, wherein each alkyl radical and each alkoxy radical are branched or straight and each alkyl radical, each alkoxy radical and each cycloalkyl group are saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms,

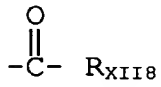
R_{XII5}, R_{XII6} and R_{XII7} are the same or different and are selected from the group which consists of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl groups, substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted cycloalkoxy-(C_{0-26})-alkyl radicals, substituted and unsubstituted alkoxy-(C_{0-26})-alkyl radicals, substituted and

unsubstituted amino groups and substituted, unsubstituted thio-(C_{0-26})-alkyl radicals and substituted or unsubstituted acyl radicals, wherein each alkyl radical, each alkoxy radical and each acyl radical is branched or straight and each alkyl radical, each alkoxy radical and each cycloalkyl group is saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms,
wherein R_{XII5} may alternatively form a ring with R_{XII1},
and R_{XII3} and R_{XII7} may comprise a carbon-oxygen-simple bond such that a ring structure is present.

The invention also includes the pharmaceutically acceptable salts, esters and salts of esters.

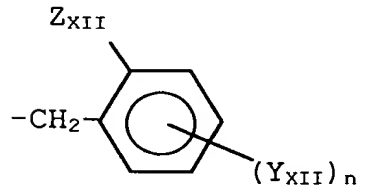
Preferably R_{XII1} and R_{XII2} are the same or different and selected from the group which consists of substituted and unsubstituted alkyl group, preferably C_1-C_4-alkyl groups.

Preferably R_{XII3} is selected from the group which consists of hydrogen, substituted and unsubstituted alkyl group, preferably C_1-C_4-alkyl groups, substituted and unsubstituted aromatic C_7-C_{14}-cycloalkyl radicals, a pyranyl group and a t-butyldimethylsilyl group and



wherein R_{XII8} is selected from the group which consists of substituted and unsubstituted, preferably with halogen substituted alkyl groups, substituted and unsubstituted cyloalkyl(C_{0-26})-alkyl radicals, substituted and unsubstituted amino groups, substituted and unsubstituted alkoxy groups, substituted and unsubstituted phenoxy groups, substituted and unsubstituted alkylthio groups, substituted and unsubstituted, preferably unsubstituted or with halogen, methyl, methoxy, nitro, amino or CF_3-groups substituted aromatic cycloalkylthio groups.

R_{XII4} is preferably selected from the group which consists of hydrogen, substituted and unsubstituted alkyl radicals, substituted and unsubstituted phenyl radicals and

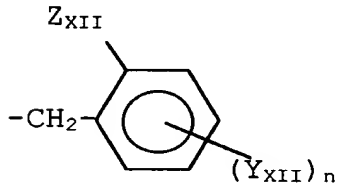


wherein Z_{XII} is selected from the group which consists of hydrogen, halogen, C_{1-4}-alkyl radicals and phenyl radicals and Y_{XII} is selected from the group which consists of hydrogen, halo-

gen, C_{1-4}-alkyl radicals, nitro radicals, methoxy radicals, methylenedioxy groups, wherein n is 0 or 1.

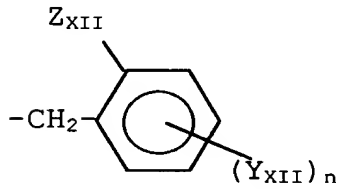
R_{XII7} is preferably selected from the group which consists of hydrogen and halogen, or R_{XII3} and R_{XII7} comprise a carbon-oxygen-simple bond, such that a ring structure is present.

Compounds are particularly preferred, in which R_{XII1} and R_{XII2} independently are selected from the group which consists of methyl and ethyl,
R_{XII4} is



and
R_{XII5} and R_{XII6} are independently selected from the group which consists of hydrogen, chlorine, bromine and methoxy groups.

In particular compounds are preferred in which R_{XII4} is



wherein Z is selected from the group which consists of 2-chloro, 2-bromo, 2-fluoro, and Y is selected from the group which consists of 4-chloro, 4-bromo, 4-fluoro, 5-fluoro and 4,5-methylenedioxy groups, wherein n is 0 or 1.

Compounds are particularly especially preferred, in which R_{XII1} and R_{XII2} are methyl groups and R_{XII3} and R_{XII7} are hydrogen or contain a carbon-oxygen-bond forming a ring structure.

Examples of preferred compounds are 3-chloro-N-(2-chlorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, N-(2-chlorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-hydroxy-N-phenyl-2,2-dimethylpropanamide, N-(2-bromophenyl)-methyl-3-chloro-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-hydroxy-2,2-dimethyl-N-(2-methylphenyl)methylpropanamide, 3-chloro-N-hydroxy-2,2-N-trimethylpropanamide, 3-chloro-N-hydroxy-2,2-dimethyl-N-(phenylmethyl)-propanamide, 3-chloro-N-(2,4-dichlorophenylmethyl)-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-(2-chlorophenyl)methyl-N-

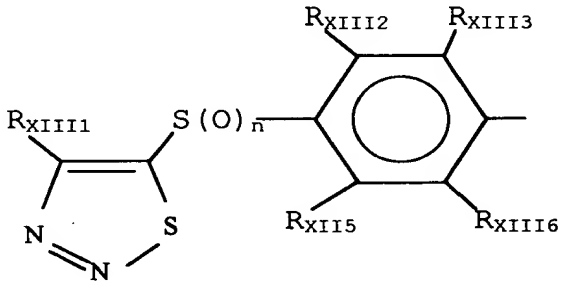
methoxy-2,2-dimethylpropanamide, 3,3-dichloro-N-(2-chlorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-(2-fluorophenyl)methyl-N-hydroxy-2,2-dimethylpropanamide, 3-bromo-N-(2-chlorophenylmethyl-N-hydroxy-2,2-dimethylpropanamide, N-benzoyloxy-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, N-acetoxy-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, N-(chloroacetoxy)-3-chloro-N-(2-chlorophenyl)methyl-2,2-dimethylpropanamide, 2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 4,4-dimethyl-2-phenyl-3-isoxazolidinone, 2-(2-bromophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 4,4-dimethyl-2-(2-methyl-phenyl)methyl-3-isoxazolidinone, 2,4-trimethyl-3-isoxazolidinone, 4,4-dimethyl-2-phenylmethyl-3-isoxazolidinone, 2-(2,4-dichlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 5-chloro-2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, 2-(2-chlorophenyl)methyl-5-methoxy-4,4-dimethyl-3-isoxazolidinone, 2-(2-fluorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone, N-[(2-chlorophenyl)methyl]-N,3-dihydroxy-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-(methylamino-carbonyloxy)propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-[(2-tetrahydropyranyl)oxyl-2,2-dimethyl-propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-[dimethyl(1,1-dimethyl-ethyl)silyloxy propanamide, 3-acetoxy-N-[(2-chlorophenoxy)-methyl]-N-hydroxy-2,2-dimethylpropan amide, 2,[(2-chloro-4-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-5-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2,4,5-trichlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-6-fluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-ethoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-phenylamino-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-hydroxy-4,4-dimethyl-3-isoxazolidinone, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-[(phenylamino)carbonyloxy]-propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-N-([(2-chlorophenyl)methyl]-2,2-dimethyl-N-phenoxycarbonyl-oxy)propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-ethoxy-carbonyloxy-2,2-dimethylpropanamide, N-benzoyloxy-3,3-dichloro-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, N-(2-bromophenyl)methyl-3,3-dichloro-N-hydroxy-2,2-dimethyl)propanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-(4-nitrobenzoyloxy)-2,2-dimethylpropanamide, 3-chloro-N-[2-chlorophenylmethyl)]-2,2-dimethyl-N-[(2-methylphenyl)carbonyloxy]propanamide, 3-chloro-N-dichloroacetoxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(4-methylphenyl)sulfonyloxy]propanamide, 3-chloro-N-[2-chloro-phenyl)methyl]-2,2-dimethyl-N-[(1,1-dimethylethyl)carbonyl-oxy]propanamide, 3-chloro-N-[2-chlorophenyl)-methyl]-2,2-dimethyl-N-(ethylthiocarbonyloxy)propanamide, 3-chloro-N-[(2,2,2-trichloroethoxy)carbonyloxy)-N-[(2-chlorophenyl)methyl]-2,3-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)aminocarbonyl-oxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-chloro-N-[(4-chlorophenyl)aminocarbonyloxy-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-

dimethyl-N-(phenylmethoxy)-propanamide, 3-chloro-N-[(2,4-dichlorophenyoxy)acetoxy)-N-[(2-chlorophenyl)methyl]-2,2-dimethyl-propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(3-trifluoromethyl)benzoyloxypropanamide, 3-chloro-N-[2-chlorophenyl)methyl]-2,2-dimethyl-N-[(4-methylphenyl)aminocarbonyl-oxy)-propanamide, 3-chloro-N-[2-chlorophenyl)methyl]-N-[(3,4-chlorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 3-chloro-N-(3-chloro-2,2-dimethyl-1-oxo-propoxy)-N-[(2-chlorophenyl)-methyl]-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)-methyl]-N-hydroxy-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)-methyl]-N-[(2-fluorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-[(4-methoxyphenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 3-chloro-N-[(2-chlorophenyl)methyl]-N-[(3-trifluormethylphenyl)-aminocarbonyloxy]-2,2-dimethylpropanamide, 3-bromo-N-[(2-chlorophenyl)methyl]-N-(methylaminocarbonyloxy)-2,2-dimethyl-propanamide, 3-bromo-N-(2-chloroacetoxy)-N-[(2-chlorophenyl)-methyl]-2,2-dimethylpropanamide, 3-chloro-N-[2,5-dichloro-(formylamino)-benzoyl]oxy-N-[(2-chlorophenyl)methyl]-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)methyl]-N-chloroacetoxy-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)-methyl]-N-(methylcarbonyloxy)-2,2-dimethylpropanamide, 3-bromo-N-[(2-bromophenyl)methyl]-N-[(2-chlorophenyl)aminocarbonyloxy]-2,2-dimethylpropanamide, 2-[(2-chlorophenyl)methyl]-N-hydroxy-2,2-dimethyl-3-methylthio-propanamide, 3-phenylcarbonyloxy)-N-[(2-chlorophenyl)-methyl]-N-hydroxy-2,2-dimethylpropanamide, 2-[(4-chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(3,4-dichlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone-5-ylacetate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone-5-ylbenzoate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone-5-yldichloroacetate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone-5-ylphenylcarbamate, 2-[(chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone-5-ylmethyl-carbamate, 2-[(2-chloro-4-cyanophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-5-methoxyphenyl) methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-4-methoxyphenyl)-methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2,4-difluorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(4-bromo-2-chlorophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-bromo-4-fluorphenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(6-chloro-1,3-benzdioxol-5-yl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-phenoxy-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(1-methylethoxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(phenylmethoxy)-3-isoxazolidinone, 2-[(2-bromophenyl)methyl]-5-chloro-4,4-dimethyl-3-isoxazolidinone, 2-[(2,5-dichlorophenyl)methyl]-4,4-dimethyl--3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-propoxy-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-propenyloxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-propinyl-oxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-4,4-dimethyl-5-(2-methoxyethoxy)-3-

isoxazolidinone, 2-[(4-fluoro-2-iodophenyl)methyl]-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-cyclopentoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-4,4-dimethyl-5-(4-nitophenoxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-cyclopropyl-methoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-bromophenyl-(methyl)]-4,4-dimethyl-5-(2-propinoxy)-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-butinoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(2-butinoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-butenoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-5-pentoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-hexoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(1-methylpropoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)methyl]-5-(3-methyl-3-butenoxy)-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chlorophenyl)-methyl]-5-butoxy-4,4-dimethyl-3-isoxazolidinone, 2-[(2-chloro-phenyl)methyl]-4,4-dimethyl-3-isoxazolidinone.

XIII. Combined preparation of lipid metabolism inhibitor with thiadiazole derivatives

The thiadiazole derivatives used according to the present invention correspond to the general formula (XIII):



(XIII)

wherein n is an integer from 0 to 4, and

wherein R_{XIII1}, R_{XIII2}, R_{XIII3}, R_{XIII4}, R_{XIII5} and R_{XIII6} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl radicals, substituted and unsubstituted alkoxy radicals, substituted and unsubstituted acyl radicals, substituted or unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted cycloalkyl-(C_{0-26})-alkoxy radicals and halogen, wherein each alkyl radical, each alkoxy radical and each acyl radical may be branched or straight and each alkyl radical, each acyl radical, each alkoxy radical and each cyclo-(C_{0-26})-alkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms.

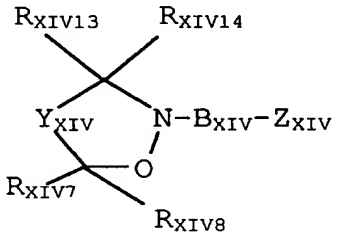
Preferably R_{XIII1} represents $COOC_2H_5$.

Furthermore compounds are preferred, in which R_{XIII2} to R_{XIII6} are selected from the group which consists of hydrogen and halogen, in particular chlorine,.

Preferably n furthermore represents 1 or 2.

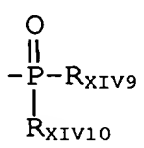
XIV. Combined preparation of lipid metabolism inhibitor and a nitrogen-oxygen-heterocycle

The compounds according to the invention contained in the pharmaceutical compositions correspond to the general formula (XIV):



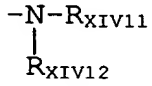
(XIV)

wherein Y_{XIV} is a C_{1-3}-alkenylene group, which is substituted with the substituents R_{XIV1} and R_{XIV2} and optionally with the substituents R_{XIV3} to R_{XIV6},
wherein R_{XIV1} to R_{XIV8} are the same or different and are selected from the group which consists of hydrogen, hydroxy, halogen, substituted and unsubstituted alkyl groups, substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted cycloalkoxy-(C_{0-26})-alkyl radicals, substituted and unsubstituted alkoxy-(C_{0-26})-alkyl radicals, substituted and unsubstituted amino groups and substituted, unsubstituted thio-(C_{0-26})-alkyl radicals, substituted and unsubstituted sulfonyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted sulfinyl-(C_{0-26})-alkyl radicals and substituted or unsubstituted acyl radicals, wherein each alkyl radical, each alkoxy radical and each acyl radical may be branched or straight and each alkyl radical, each alkoxy radical and each cycloalkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms and
R_{XIV13} and R_{XIV14} are defined the same as R_{XIV1} to R_{XIV8} or together form an oxo group,
wherein Z_{XIV} represents the organophosphorus group



wherein R_{XIV9} and R_{XIV10} are the same or different and are selected from the group which con-

sists of hydrogen, substituted and unsubstituted (C_{1-26})-alkyl groups, substituted and unsubstituted hydroxy-(C_{1-26})-alkyl radicals, substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted acyl, halogen, OX_{XIV9} or OX_{XIV10}, wherein each alkyl radical, each alkoxy radical and each acyl radical may be branched or straight and each alkyl radical, each alkoxy radical and each cycloalkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms, wherein X_{XIV9} or X_{XIV10} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted (C_{1-26})-alkyl groups, substituted and unsubstituted hydroxy-(C_{1-26})-alkyl radicals, substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted acyl, a silyl, a cation of an organic and inorganic base, in particular a metal of the first, second or third main group of the periodic system, ammonium, substituted ammonium and ammonium compounds which derive from ethylene diamine or amino acids, wherein each alkyl radical, each alkoxy radical and each acyl radical may be branched or straight and each alkyl radical, each alkoxy radical and each cycloalkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms,
or wherein Z_{XIV} represents the amino group



wherein R_{XIV11} and R_{XIV12} are the same or different and are selected from the group which consists of hydrogen, substituted and unsubstituted alkyl groups, substituted and unsubstituted cycloalkyl-(C_{0-26})-alkyl radicals, substituted and unsubstituted cycloalkoxy-(C_{0-26})-alkyl radicals, substituted and unsubstituted alkoxy-(C_{0-26})-alkyl radicals and substituted or unsubstituted acyl radicals, wherein each alkyl radical, each alkoxy radical and each acyl radical may be branched or straight and each alkyl radical, each alkoxy radical and each cycloalkyl group may be saturated or unsaturated with one or more double or triple bonds and one or two carbon atoms of the cycloalkyl radicals may be replaced by nitrogen, oxygen or sulfur atoms, wherein B_{XIV} is selected from the group which consists of substituted and unsubstituted C_{1-26}-alkenylene groups, wherein a C-atom may be replaced by an oxygen atom and a C-atom may be replaced by a sulfur atom or two C-atoms may be replaced by an S-hetrocycle and wherein each alkenylene radical may be branched or straight and saturated or unsaturated with one or more double or triple bonds and may be substituted with one or more hydroxy groups, halogen groups or oxo groups.

Preferably R_{XIV13} and R_{XIV14} together form an oxo group in α-position regarding the nitrogen atom.

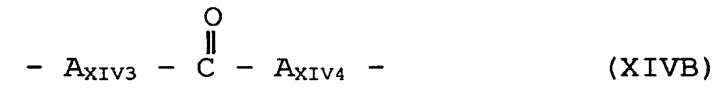
Preferably Y_{XIV} represents a methylene group, which is particularly preferably substituted with two methyl groups.

Furthermore compounds are advantageous, in which B_{XIV} represents the ether group (XIVA)

$$- A_{XIV1} - O - A_{XIV2} - \qquad \text{(XIVA)}$$

wherein A_{XIV1} is absent or a (C_{1-9})-alkylene radical,
and A_{XIV2} is absent or selected from the group which consists of (C_{1-9})-alkylene radicals, a sulfur atom and a (C_{3-8})-heterocycle, which comprises at least one sulfur atom. Particularly preferably A_{XIV1} and A_{XIV2} each represent a methylene group.

Also compounds are advantageous, in which B_{XIV} represents the keto group (XIVB)



$$- A_{XIV3} - C(=O) - A_{XIV4} - \qquad \text{(XIVB)}$$

wherein A_{XIV3} and A_{XIV4}, out of which one or both may be absent, are the same or different and are selected from the group which consists of (C_{1-9})-alkylene radicals,
wherein all (C_{1-9})-alkylene radicals may be branched or straight, may contain one or more double bonds or may be substituted with a hydroxy group or a halogen group. Particularly preferred A_{XIV3} is absent and A_{XIV4} represents a methylene or an ethylene group.

Preferably B_{XIV} is further a 2-hydroxypropylene group.

R_{XIV9} and R_{XIV10} preferably represent OX_{XIV9} and OX_{XIV10}, wherein X_{XIV9} and X_{XIV10} are the same or different and are selected from the group which consists of a metal of the first, second or third main group of the periodic system, in particular sodium and potassium, and methyl, ethyl.

Special features of the above definitions and suitable examples thereof are given below:

„Acyl" is a substituent which originates from an acid such as from an organic carboxylic acid, carbonic acid, carbamic acid or the thioacid or imidic acid corresponding to the individually present acids, or from an organic sulfonic acid, wherein in each case these acids comprise aliphatic, aromatic and/or heterocyclic groups in the molecule as well as carbamoyl or carbamimidoyl.

Suitable examples of these acyl groups were given below:.

Acyl radicals originating from aliphatic acid are designated as aliphatic acyl groups and include:
Alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl etc.);
alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl etc.);
alkylthioalkanoyl (for example methylthioacetyl, ethylthioacetyl etc.)
alkane sulfonyl (for example mesyl, ethane sulfonyl, propane sulfonyl etc.);
alkoxycarbonyl (for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl etc.);
alkylcarbamoyl (for example methylcarbamoyl etc.);
(N-alkyl)-thiocarbamoyl (for example (N-methyl)-thiocarbamoyl etc.);
alkylcarbamimidoyl (for example methylcarbamimidoyl etc.);
oxalo;
alkoxalyl (for example methoxalyl, ethoxalyl, propoxalyl etc.).

In the above examples of aliphatic acyl groups the aliphatic hydrocarbon part, in particular the alkyl group and the alkane radical may optionally contain one or more suitable substituents, such as amino, halogen (for example fluorine, chlorine, bromine etc.), hydroxy, hydroxyimino, carboxy, alkoxy (for example methoxy, ethoxy, propoxy etc.), alkoxycarbonyl, acylamino (for example benzyloxycarbonylamino etc.), acyloxy (for example acetoxy, benzoyloxy etc.) and the like. Preferred aliphatic acyl radicals with such substituents are for example alkanoyls substituted with amino, carboxy, amino and carboxy, halogen, acylamino or the like.

Acyl radicals originating from an acid with substituted or unsubstituted aryl groups, wherein the aryl group may comprise phenyl, toluyl, xylyl, naphthyl and the like are designated as aromatic acyl radicals. Suitable examples are given below:
Aroyl (for example benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl etc.);
Aralkanoyl (for example phenylacetyl etc.);
Aralkenoyl (for example cinnamoyl etc.);
Aryloxyalkanoyl (for example phenoxyacetyl etc.);
Arylthioalkanoyl (for example phenylthioacetyl etc.);
Arylaminoalkanoyl (for example N-phenylglycyl, etc.);
Arene sulfonyl (for example benzene sulfonyl, tosyl bzw. toluene sulfonyl, naphthalene sulfonyl etc.);
Aryloxycarbonyl (for example phenoxycarbonyl, naphthyl-oxycarbonyl etc.);
Aralkoxycarbonyl (for example benzyloxycarbonyl etc.);
Arylcarbamoyl (for example phenylcarbamoyl, naphthylcarbamoyl etc.);
Arylglyoxyloyl (for example phenylglyoxyloyl etc.).

In the present examples of aromatic acyl radicals the aromatic hydrocarbon part (in particular the aryl radical) and/or the aliphatic hydrocarbon part (in particular the alkane radical) may optionally contain one or more suitable substituents, such as those which were already mentioned as suitable substituents of the alkyl group and the alkane radical. In particular and as an example for preferred aromatic acyl radicals with particular substituents, aroyl substituted with halogen and hydroxy or by halogen and acyloxy and acyloxy and aralkanoyl substituted with hydroxy, hydroxyimino, dihalogenalkanoyloxyimino are mentioned as well as arylthiocarbamoyl (for example phenylthiocarbamoyl etc.);
arylcarbamimidoyl (for example phenylcarbamimidoyl etc.).

A heterocyclic acyl radical is understood to be an acyl radical which originates from an acid with heterocyclic group. These include:

heterocyclic carbonyl in which the heterocyclic radical is an aromatic or aliphatic 5 to 6 membered heterocycle and has at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenyl, furoyl, pyrrolcarbonyl, nicotinoyl etc.);

heterocyclic alkanoyl, in which the heterocyclic radical is 5 to 6 membered and has at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenyl-acetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl, 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl etc.) and the like.

In the above examples of heterocyclic acyl radicals the heterocycles and/or the aliphatic hydrocarbon part may optionally contain one or more suitable substituents, such as the same as those which were mentioned as suitable for alkyl and alkane groups.

„Alkyl" is a straight- or branched-chain alkyl radical having up to 9 carbon atoms, unless defined otherwise, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, hexyl and the like.

„Alkenyl" includes straight- or branched-chain alkenyl groups with up to 9 carbon atoms, unless defined otherwise, for example vinyl, propenyl (for example 1-propenyl, 2-propenyl), 1-methylpropenyl, 2-methylpropenyl, butenyl, 2-ethylpropenyl, pentenyl, hexenyl.

„Alkynyl" includes straight- or branched-chain alkynyl radicals having up to 9 carbon atoms, unless defined otherwise.

Cycloalkyl preferably represents an optionally substituted C_3 to C_7 cycloalkyl. alkyl, alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.),

nitro and the like are inter alia suitable as possible substituents.

Aryl is an aromatic hydrocarbon radical such as phenyl, naphthyl etc., which may optionally contain one or more suitable substituents such as alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

„Aralkyl" includes mono-, di-, triphenylalkyls such as benzyl, phenethyl, benzhydryl, trityl and the like, wherein the aromatic part may optionally contain one or more suitable substituents such as alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

„Alkylene" includes straight- or branched-chain alkylene groups, which contain up to 9 carbon atoms and may be represented by the formula $-(C_nH_{2n})-$
in which n is an integer from 1 to 9, such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, 1-methyltrimethylene, 2-ethylethylene, pentamethylene, 2-methyltetramethylene, isopropylethylene, hexamethylene, and the like. Preferred alkylene radicals contain up to 4 carbon atoms and radicals with 3 carbon atoms, such as for example trimethylene are particularly preferred.

„Alkenylene" includes straight- or branched-chain alkenylene groups with up to 9 carbon atoms which may be reproduced by the formula:
$-(C_nH_{2n-2})-$
in which n is an integer from 2 to 9, for example vinylene, propenylene (for example 1-propenylene, 2-propenylene), 1-methylpropenylene, 2-methylpropenylene, butenylene, 2-ethylpropenylene, pentenylene, hexenylene and the like. The alkenylene radical may particularly preferably contain up to 5 carbon atoms and in particular 3 carbon atoms, for example 1-propenylene.

„Hydroxyalkylene" may include straight- or branched-chain alkylene radicals which contain up to 9 carbon atoms, wherein one or more selected carbon atoms are substituted with a hydroxy group. These radicals may be represented by the formula:
$-(C_nH_{2n-z})(OH)_z-$
in which n is an integer from 1 to 9 and z is an integer, to which $z \leq n$ applies. Suitable examples of such hydroxyalkylene groups include hydroxymethylene, hydroxyethylene (for example 1-hydroxyethylene and 2-hydroxyethylene), hydroxytrimethylene (for example 1-hydroxytrimethylene, 2-hydroxytrimethylene and 3-hydroxytrimethylene), hydroxytetramethylene (for example 2-hydroxytetramethylene), 2-hydroxy-2-methyltrimethylene, hydroxypentamethylene (for example 2-hydroxypentamethylene), hydroxyhexamethylene (for example 2-hydroxyhexamethylene) and the like. A lower hydroxyalkylene with up to 4 car-

bon atoms is particularly preferred and in particular one with 3 carbon atoms for example 2-hydroxytrimethylen.

„Alkyleneamine" includes straight- or branched-chain alkylene amine groups, which contain up to 9 carbon atoms and may be represented by the formula:
$-(C_nH_{2n})-N-(C_mH_{2m})-$
in which n and m may be the same or different and be an integer from 0 to 9, to which $1 \leq n + m \leq 9$ applies, such as methyleneamine, ethyleneamine, dimethylene amine, trimethylene amine, methylene ethyleneamine, tetramethylene amine, 1-methyltrimethylene amine, 2-ethylethylene amine, ethylenemethylene amine, pentamethylene amine, 2-methyltetramethylene amine, isopropylethylene amine, hexamethylene amine, and the like. Preferred alkylene amine radicals contain 2 carbon atoms, which are end positioned. Dimethylene amine is particularly preferred. The hydrogen atoms may be replaced by substituents, for example halogen radicals.

„Alkyleneimine" includes straight- or branched-chain alkyleneimine groups, which contain up to 9 carbon atoms and may be represented by the formula
$-(C_nH_{2n-1})=N-(C_mH_{2m})-$or
the formula $-(C_nH_{2n})-N=(C_mH_{2m-1})-$
in which n and m may be the same or different and are an integer from 0 to 9, to which $1 \leq n + m \leq 9$ applies, such as methyleneimine, ethyleneimine, dimethyleneimine, trimethyleneimine, methylenethyleneimine, tetramethyleneimine, 1-methyltrimethyleneimine, 2-ethylethyleneimine, ethylenemethyleneimine, pentamethyleneimine, 2-methyltetramethyleneimine, isopropylethyleneimine, hexamethyleneimine, and the like. Preferred alkylene imine radicals contain 2 carbon atoms, which are end positioned. Dimethyleneimine is particularly preferred. The hydrogen atoms may also be replaced by substituents, for example by halogen radicals.

„Alkenyleneamine" includes straight- or branched-chain alkenylene amine groups having up to 9 carbon atoms, which may be represented by the formula
$-(C_nH_{2n-2})-N-(C_mH_{2m-2})-$; $-(C_oH_{2o})-N-(C_nH_{2n-2})-$; $-(C_nH_{2n-2})-N-(C_oH_{2o})-$
in which n and m are the same or different and are an integer from 2 to 9, to which $m + n \leq 9$ applies, and o is a number between 0 and 7, to which $o + n \leq 9$ applies, for example vinyleneamine, methylenevinyleneamine, divinyleneamine, propenyleneamine (for example 1-propenyleneamine, 2-propenyleneamine), methylenpropenyleneamine, 1-methylpropenyleneamine, 2-methylpropenyleneamine, butenyleneamine, 2-ethylenepropenyleneamine, pentenyleneamine, hexenyleneamine, vinylmethyleneamine and the like. The hydrogen atoms may also be replaced by substituents, for example by halogen radicals.

„Alkenyleneimine" includes straight- or branched-chain alkenylene imine groups having up to 9 carbon atoms, which may be represented by the formula
$-(C_nH_{2n-3})=N-(C_mH_{2m-2})-$; $-(C_oH_{2o-1})=N-(C_mH_{2m-2})-$; $-(C_nH_{2n-3})=N-(C_oH_{2o})-$;
$-(C_nH_{2n-2})=N-(C_mH_{2m-3})-$; $-(C_oH_{2o})-N=(C_mH_{2m-3})-$; $-(C_nH_{2n-2})-N=(C_oH_{2o-1})-$
in which n and m are the same or different and are an integer from 2 to 9, to which $m + n \leq 9$ applies, and o is a number from 0 to 7, to which $o + n \leq 9$ applies, for example vinyleneimine, methylenevinyleneimine, ethylenevinyleneimine, propenyleneimine (for example 1-propenylene imine, 2-propenylene imine), methylenepropenyleneimine, 1-methylpropenyleneimine, 2-methylpropenyleneimine, butenyleneimine, 2-ethylenepropenyleneimine, pentenyleneimine, hexenyleneimine, vinylemethyleneimine and the like. The hydrogen atoms may also be replaced by substituents, for example by halogen radicals.

„Hydroxyalkyleneamine" may be straight- or branched-chain alkylene radicals which contain up to 9 carbon atoms, wherein at least one selected carbon atom is substituted with a hydroxy group; these radicals being represented by the formula
$-(C_nH_{2n-z})(OH)_z-N-(C_mH_{2m-y})(OH)_y$
in which n and m are the same or different and are an integer from 0 to 9, to which $1 \leq n + m \leq 9$ applies, and z and y are the same or different and are an integer, to which $0 \leq z \leq n$ and $0 \leq y \leq m$ and $y + z \geq 1$ applies. Suitable examples of such hydroxyalkyleneamine groups include hydroxymethyleneamine, hydroxyethyleneamine (for example 1-hydroxyethylenamine and 2-hydroxyethyleneamine), hydroxytrimethyleneamine (for example 1-hydroxytrimethylene, 2-hydroxytrimethylenamine and 3-hydroxytrimethyleneamine), hydroxytetramethylene amine (for example 2-hydroxytetramethyleneamine), 2-hydroxy-2-methyltrimethyleneamine, hydroxypentamethyleneamine (for example 2-hydroxypentamethyleneamine), hydroxyhexamethyleneamine (for example 2-hydroxyhexamethyleneamine), methylenehydroxymethyleneamine, methylenehydroxyethyleneamine and the like. A lower hydroxyalkylene amine with 2 carbon atoms and one nitrogen atom is particularly preferred wherein both carbon atoms are end positioned. The hydrogen atoms may also be replaced by substituents, for example by halogen radicals.

„Hydroxyalkyleneimine" includes straight- or branched-chain alkylene radicals, which contain up to 9 carbon atoms, wherein at least one selected carbon atom is substituted with a hydroxy group. These radicals may be represented by the formula
$-(C_nH_{2n-z-1})(OH)_z=N-(C_mH_{2m-y})(OH)_y$; $-(C_nH_{2n-z-1})(OH)_z-N=(C_mH_{2m-y})(OH)_y$
in which n and m are the same or different and are an integer from 0 to 9, to which $1 \leq n + m \leq 9$ applies, and z and y are the same or different and an integer, to which $0 \leq z \leq n-1$ and $0 \leq y \leq m-1$ and $y + z \geq 1$ applies. Suitable examples of such hydroxyalkyleneimine groups include hydroxymethyleneimine, hydroxyethyleneimine (for example 1-hydroxyethyleneimine and 2-hydroxyethyleneimine), hydroxytrimethyleneimine (for example 1-hydroxytri-

methyleneimine, 2-hydroxytrimethyleneimine and 3-hydroxytrimethyleneimine), hydroxy-tetramethyleneimine (for example 2-hydroxy-tetramethyleneimine), 2-hydroxy-2-methyl-trimethylene imine, hydroxypentamethyleneimine (for example 2-hydroxypentamethylene-imine), hydroxyhexamethyleneimine (for example 2-hydroxyhexamethyleneimine), methyle-nehydroxymethyleneimine, methylenehydroxyethyleneimine and the like. A lower hydroxyalkyleneimine with 2 carbon atoms and a nitrogen atom, wherein the two carbon atoms are end positioned, is particularly preferred. The hydrogen atoms may also be replaced by substituents, for example by halogen radicals.

The 5 and 6 membered cyclic compounds, which are represented by B_{IV} may be aromatic or aliphatic and may be substituted for example by alkyl groups with up to 7 carbon atoms and hydroxy groups.

The 5 and 6 membered heterocyclic compounds, which may be represented by R_{VIII1} and R_{VIII2} as well as R_{X1} and R_{X2}, and which contain beside carbon one or two nitrogen, oxygen or sulfur atoms as a ring member, may be saturated or unsaturated.

„Alkoxy radical" is, unless defined otherwise, a straight- or branched-chain alkoxy radical having up to 26 carbon atoms, such as a methoxy, ethoxy radicals, etc.. It may be substituted for example by hydroxy, amino, halogen, oxo groups and alkoxy radicals, such as methoxy-, ethoxy radicals.

„Alkoxy-(C_{0-26})-alkyl radicals" are alkoxy radicals, which may also be bound to the basic structure upon an alkyl radical. The alkyl- and alkoxy groups are defined the same as above.

„Cycloalkyl-(C_{0-26})-alkyl radicals" are cyclic compounds having 3 to 8 carbon atoms, unless defined otherwise, which are bound to the basic structure directly or upon an alkylene radical. The alkylene radical may be branched, straight and saturated or unsaturated with double bonds. Possible substituents of the cycloalkyl radicals are inter alia alkoxy radicals, alkyl radicals, hydroxy radicals, halogen radicals, amino radicals, oxo radicals. Providing a respective number of double bonds, the cycloalkyl radicals may also be aromatic, i.e. may be aryl-(C_{0-26})-alkyl radicals (for example phenyl, pyridyl, naphthyl etc.). In particular the aromatic cyclic compounds may further contain substituents, such as nitro groups and CF_3 and phenyl radicals.

„Cycloalkoxy-(C_{0-26})-alkyl radicals" are cyclic compounds with 3 to 8 carbon atoms, which are bound to the basic structure directly at an oxygen or upon an alkylene radical. The alkylene radical may be branched, straight and may be saturated or unsaturated with double bonds. Possible substituents of the cycloalkyl radicals are inter alia radicals (also alkylenedi-

oxy radicals, such as methylenedioxy), alkyl radicals, hydroxy radicals, halogen radicals, amino radicals, oxo radicals. Providing the respective number of double bonds the cycloalkyl radicals may also be multicycles and aromatic (for example phenoxy, pyridoxy, naphthoxy etc.). In particular the aromatic cyclic compounds further may contain substituents, such as nitro groups, CF_3-groups and phenyl radicals.

For example the „amino radicals" may be substituted for example with the with the above defined alkyl radicals or cycloalkyl-(C_{0-26})-alkyl radicals.

„Amino-(C_{0-26})-alkyl radicals" are amino radicals, which also may be bound to the basic structure upon an alkyl radical. The alkyl and amino groups are defined the same as above.

„Silyl radicals" may be substituted for example with the above defined alkyl radicals or cycloalkyl-(C_{0-26})-alkyl radicals.

„Silyl"-(C_{0-26})-alkyl radicals" are silyl radicals, which also may be bound to the basic structure upon an alkyl radical. The alkyl and silyl groups are defined the same as above.

„Thio-(C_{0-26})-alkyl radicals" may be substituted for example with the above defined alkyl radicals or cycloalkyl-(C_{0-26})-alkyl radicals. The (C_{0-26})-alkyl groups are straight- or branched-chain alkylene radicals such as methylene, ethylene, propylene, isopropylene, butylene, isobutylene, tert.-butylene, pentylene, hexylene and the like. They may contain double or triple bonds and be substituted for example with hydroxy, amino, halogen (for example fluorine, bromine, chlorine), oxo radicals and alkoxy radicals, such as methoxy, ethoxy radicals.

Preferably, the radicals X_{I3} to X_{VII3} and X_{I4} to X_{VII4} as well as R_{VIII5}, R_{IX11}, X_{XI3} and X_{XI4}, X_{III} and X_{II2} may be selected such, that esters form on the phosphono group or the sulfonyl group. Suitable examples of esters of the compounds used according to the present invention are suitable mono and diesters, and preferred examples of such esters includes alkylester (for example methylester, ethylester, propylester, isopropylester, butylester, isobutylester, hexylester etc.);
aralkyl ester (benzyl ester, phenethyl ester, benzohydryl ester, trityl ester etc.);
aryl ester (for example phenyl ester, toluyl ester, naphthyl ester etc.); aroylalkyl ester (for example phenacyl ester etc.); and silylester (for example of trialkylhalogensilyl, dialkyldihalogensilyl, alkyltrihalogensilyl, dialkylarylhalogensilyl, trialkoxyhalogensilyl, dialkylaralkylhalogensilyl, dialkoxydihalogensilyl, trialkoxyhalogensilyl etc.) and the like.

With the above esters the alkane and/or arene part may optionally contain at least one suitable substituent such as halogen, alkoxy, hydroxy, nitro or the like.

X_{I3} to X_{VII3} and X_{I4} to X_{VII4} as well as X_{XI3} and X_{XI4}, X_{II1} and X_{II2} are preferably a metal from the first, second or third main group of the periodic system, ammonium, substituted ammonium, or ammonium compounds, which derive from ethylene diamine or amino acids. In other words the salt compounds of the ammonium phosphonic acid derivatives with organic or inorganic bases (for example sodium salt, potassium salt, calcium salt, aluminium salt, ammonium salt, magnesium salt, triethylamine salt, ethanolamine salt, dicyclohexylamine salt, ethylenediamine salt, N,N'-dibenzylethylenedi amine salt etc.) as well as salts with amino acids (for example arginine salt, aspartic acid salt, glutamic acid salt etc.) and the like.

The compounds according to the invention in accordance with the formulae (I) to (XIV) permit for example the emergence of spatial isomers for groups containing double bonds or chiral groups R or A or B or Y or Z or X. The use of the compounds according to the invention includes all spatial isomers both as pure substances and in form of their mixtures.

Pharmaceutically acceptable salts of the aminohydrophosphonic acid derivative include salts, which form the compounds according to the invention in their protonised form as an ammonium salt of inorganic or organic acids, such as hydrochloric acid, sulfur acid, citric acid, maleic acid, fumaric acid, tartaric acid, p-toluene sulfonic acid.

Salts which are formed by suitable selection of X_3 (X_{I3} to X_{V3}) and X_4 (X_{I4} to X_{V4}) as well as X_{II1} and X_{II2} are especially suited, such as sodium salt, potassium salt, calcium salt, ammonium salt, ethanolamine salt, triethylamine salt, dicyclohexylamine salt and salts of amino acid such as arginine salt, aspartic acid salt, glutamic acid salt.

The lipid metabolism inhibitors according to the invention contain one or more inhibitors of lipid metabolism. Inhibitors may be used which control the intake of fats as well as inhibitors, which control the synthesis of fats. The inhibitors include anion exchangers, preferably cholestyr amine and colestipol, β-sitosterol, nicotinic acids and their derivatives, such as nicotinyl alcohol, clofibrate and their derivatives, such as clofibrin acid ethylester, as well as their analogues, such as bezafibrate, fenofibrate and gemfibrozil, and probucol.

The inhibitors, which control the synthesis of fats, include HMG-CoA synthetase inhibitors, HMG-CoA reductase inhibitors, preferably lovastatin, mevastatin, simvastatin, fluvastatin, atorvastatin, pravastatin and cerivastatin, inhibitors the squalene synthetase, preferably pyrophosphate, pyrophosphate derivatives, bisphosphonic acid derivatives, phosphinylmethylphosphonic acid derivatives, phosphinylformyl derivatives, phosphonocarboxyl derivatives, phosphonosulfonic acid derivatives, phosphinylmethylphosphonic acid derivatives, inhibitors of the squalene monooxygenase and other inhibitors of the synthesis of cholesterol.

Inhibitors of the HMG-CoA-reductase and inhibitors of the squalene synthetase are especially preferred.

Out of the bisphosphonates clodronate, etidronate, pamidronate, ibandronate, alendronate, zoledronate, risedronate, tiludronate and cimadronate are especially preferred.

Upon simultaneous, separate or successive administration together with inhibitors of lipid metabolism synthesis the infectiously active compounds and their esters as well as their salts show a strong cytotoxic efficacy against unicellular and multicellular parasites, fungi, bacteria and cells infected by viruses. The compounds according to the invention are usable in the treatment of infectious diseases which are caused by parasites, fungi, bacteria or viruses in humans and animals. The compounds are also suitable for the use for preventing these diseases.

The lipid metabolism inhibitors are effective against unicellular parasites (protozoa), in particular against pathogens of malaria and the sleeping sickness as well as the Chagas' disease, the toxoplasmosis, amoebic dysentery, leishmaniasis, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiasis, sarcocystosis, acanthamebiasis, naegleriasis, coccidiosis, giardiasis and lambliosis.

Therefore, they are particularly suitable as malaria prophylactics and as prophylactics of sleeping sickness as well as the Chagas' disease, toxoplasmosis, amoebic dysentery, leishmaniasis, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiasis, sarcocystosis, acanthamebiasis, naegleriasis, coccidiosis, giardiasis and lambliosis.

The lipid metabolism inhibitors according to the invention may in particular be used against the following bacteria:

Bacteria of the family Propionibacteriaceae, in particular the genus Propionibacterium, in particular the species Propionibacterium acnes; bacteria of the family Actinomycetaceae, in particular the genus Actinomyces; bacteria of the genus Corynebacterium, in particular the species Corynebacterium diphteriae and Corynebacterium pseudotuberculosis; bacteria of the family Mycobacteriaceae, the genus Mycobacterium, in particular the species Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium avium; bacteria of the family Chlamydiaceae, in particular the species Chlamydia trachomatis and Chlamydia psittaci; bacteria of the genus Listeria, in particular the species Listeria monocytogenes; bacteria of the species Erysipelthrix rhusiopathiae; bacteria of the genus Clostridium; bacteria of the genus Yersinia, the species Yersinia pestis, Yersinia pseudotuberculosis, Yer-

sinia enterocolitica and Yersinia ruckeri; bacteria of the family Mycoplasmataceae, the genus Mycoplasma and Ureaplasma, in particular the species Mycoplasma pneumoniae; bacteria of the genus Brucella; bacteria of the genus Bordetella; bacteria of the family Neiseriaceae, in particular the genuses Neisseria and Moraxella, in particular the species Neisseria meningitides, Neisseria gonorrhoeae and Moraxella bovis; bacteria of the family Vibrionaceae, in particular the genuses Vibrio, Aeromonas, Plesiomonas and Photobacterium, in particular the species Vibrio cholerae, Vibrio anguillarum and Aeromonas salmonicidas; bacteria of the genus Campylobacter, in particular the species Campylobacter jejuni, Campylobacter coli and Campylobacter fetus; bacteria of the genus Helicobacter, in particular the species Helicobacter pylori; bacteria of the families Spirochaetaceae and the Leptospiraceae, in particular the genus Treponema, Borrelia and Leptospira, in particular Borrelia burgdorferi; bacteria of the genus Actinobacillus; bacteria of the family Legionellaceae, the genus Legionella; bacteria of the family Rickettsiaceae and family Bartonellaceae; bacteria of the genus Nocardia and Rhodococcus; bacteria of the genus Dermatophilus; bacteria of the family Pseudomonadaceae, in particular the genuses Pseudomonas and Xanthomonas; bacteria of the family Enterobacteriaceae, in particular the genuses Escherichia, Klebsiella, Proteus, Providencia, Salmonella, Serratia and Shigella; bacteria of the family Pasteurellaceae, in particular the genus Haemophilus; bacteria of the family Micrococcaceae, in particular the genus Micrococcus and Staphylococcus; bacteria of the family Streptococcaceae, in particular the genus Streptococcus and Enterococcus and bacteria of the family Bacillaceae, in particular the genus bacillus and clostridium.

Accordingly, the lipid metabolism inhibitors according to the invention are suitable for treatment of diphtheria, acne vulgaris, listeriosis, erysipelas in animals, gas gangrene in humans and in animals, diseases in humans and animals caused by clostridium septicum, tuberculosis in humans and animals, leprosy, and further mycobacteriosis in humans and animals, paratuberculosis in animals, pestis, mesenterial lymphadenitis and pseudotuberkulosis in humans and animals, cholera, legionnaires disease, borrelioses in humans and animals, leptospiroses in humans and animals, syphilis, campylobacter enteritides in humans and animals, moraxella keratoconjunctivitis and serositis in animals, brucelloses in animals and in humans, anthrax in humans and animals, actinomycosis in humans and animals, streptotrichosis, psittakosis/ornithosis in animals, and Q-fever and ehrlichiosis.

Further the use is advantageous in helicobacter eradication therapy of ulcera of the gastroenteric tract.

Further combinations with an additional antibiotic may also be used for treatment of the above mentioned diseases. As lipid metabolism inhibitors with other antiinfective agents in particular isoniazide, rifampicin, ethambutol, pyrazinamide, streptomycin, protionamide and

dapson are suitable for the treatment of tuberculosis.

The lipid metabolism inhibitors according to the invention may furthermore be used in particular in infections with following viruses:
Parvoviridae: parvo viruses, dependo viruses, Denso viruses; Adenoviridae: adeno viruses, mastadeno viruses, aviadeno viruses; Papovaviridae: papova viruses, in particular papilloma viruses (so called wart viruses), Polyoma viruses, in particular JC virus, BK virus, and miopapova viruses; herpes viruses: all herpes viruses, in particular herpes simplex viruses, the varizella-zoster viruses, human cytomegalo virus, Epstein-Barr viruses, all human herpes viruses, human herpes virus 6, human herpes virus 7, human herpes virus 8; Poxviridae: pox viruses, orthopox, parapox, molluscum contagiosum virus, avipox viruses, capripox viruses, leporipox viruses; all primary hepatotropic viruses, Hepatitis viruses: hepatitis A viruses, hepatitis B viruses, hepatitis C viruses, hepatitis D viruses, hepatitis E viruses, hepatitis F viruses, hepatitis G viruses; Hepadna viruses: all hepatitis viruses, hepatitis B virus, hepatitis D viruses; Picornaviridae: picorna viruses, all entero viruses, all polio viruses, all coxsackie viruses, all echo viruses, all rhino viruses, hepatitis A virus, aphtho viruses; Calciviridae: hepatitis E viruses; Reoviridae: reo viruses, orbi viruses, rota viruses; Togaviridae: toga viruses, alpha viruses, rubi viruses, pesti viruses, rubella virus; Flaviviridae: flavi viruses, ESME virus, hepatitis-C-Virus; Orthomyxoviridae: all influenza viruses; Paramyxoviridae: paramyxo viruses, morbilli virus, pneumo virus, measles virus, mumps virus; Rhabdoviridae: rhabdo viruses, rabies virus, lyssa virus, viscula stomatitis virus; Corona viridae: corona viruses; Bunyaviridae: bunya viruses, nairo virus, phlebo virus, uuku virus, hanta virus; Arenaviridae: arena viruses, lymphocytic choriomeningitis-virus; Retroviridae: retro viruses, all HTL viruses, human T-cell leukaemia virus, oncorna viruses, spuma viruses, lenti viruses, all HI-viruses; Filoviridae: Marburg and Ebola virus; Slow-virus-infections, prions; Onco viruses, leukemia viruses.

The preparations used according to the invention are therefore suitable for fighting the following viral infections:
Eradication of papilloma viruses to prevent tumors, in particular tumors in the sexual organs caused by papilloma viruses in humans, eradication of JC viruses and BK viruses, eradication of herpes viruses, eradication of human herpes viruses 8 for the treatment of Kaposi`s sarcoma, eradication of cytomegalo viruses before transplants, eradication of Eppstein-Barr viruses before transplants and to prevent tumors associated with Eppstein-Barr viruses, eradication of hepatitis viruses for the treatment of chronic liver diseases and for the prevention of tumors of the liver and cirrhosis of the liver, eradication of coxsackie viruses patients with cardiomyopathy, eradication of coxsackie viruses in diabetes mellitus patients, eradication of immune system debilitating viruses in humans and animals, treatment of secondary infections in AIDS-patients, treatment of inflammations of viral origin of the respiratory tract (larynx

papillomas, hyberplasias, rhinitis, pharyngitis, bronchitis, pneumonias), of the sensory organs (Keratoconjunctivitis), of the nervous system (poliomyelitis, meningoenzephalitis, encephalitis, subacute sklerosing panencephalitis SSPE, progressive multifocal leukoencephalopathie, lymphocytic choriomeningitis), of the gastro-intestinal tract (stomatitis, gingivostomatitis, oesophagitis, gastritis, gastroenteritis, diarrhoea-causing diseases), the liver and the gall bladder system (hepatitis, cholangitis, hepatocellular carcinoma), of the lymphatic tissue (mononucleosis, lymphadenitis), of the haematopoetic system, of the sexual organs (mumpsorchitis), of the skin (warts, dermatitis, herpes labialis, heat rush, herpes zoster, shingles), of the mucous membranes (papillomas, conjunctiva papillomas, hyperplasias, dysplasias), of the heart/blood vessel system (arteriitis, myocarditis, endocarditis, pericarditis), the kidney/urinary tract systems, of the sexual organs (anogenital lesions, warts, genital warts, acute condylomas, displasias, papillomas, cervix dysplasias, condylomata acuminata, epidermodysplasia verruci formis), of the organs of motion (myositis, myalgien), treatment of foot and mouth diseases in cloven-hoofed animals, of Colorado tick fever, of Dengue-syndrome, of haemorrhagic fever, of early summer meningoencephalitis (FSME) and of yellow fever.

The agents are suited for combination with other agents with antiviral characteristics.

The compounds used according to the invention which generally include pharmaceutically acceptable salts, esters, a salt of such an esters or else compounds which upon application provide the compounds use according to the invention metabolic products or decomposition products, also called "prodrugs" may all be prepared for administration like known anti-infectious agents in any suitable manner (mixed with non-toxic pharmaceutically acceptable carriers).

The combined preparation used according to the invention may be administered together with non-toxic, inert pharmaceutically suitable carriers. These are understood to mean solid, semi-solid or liquid diluents, fillers and formulation auxiliary agents of all kinds.

Tablets, dragees, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays are mentioned as pharmaceutical preparations. Tablets, dragees, capsules, pills and granules may contain in addition to the conventional excipients the active ingredient, such as (a) fillers and diluents, for example starches, lactose, cane sugar, glucose, mannitol and silicic acid, (b) binders, for example carboxymethylcellulosis, alginate, gelatine, polyvinylpyrrolidone, (c) moisture-retaining agents, for example glycerol, (d) dispersing agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) solution retarders, for example paraffin and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorption agents, e.g. kaolin and betonite and (i) lubricants, for

example talcum, calcium and magnesium stearate and solid polyethylene glycol or mixtures of the substances listed under (a) to (i). The inventive compounds may furthermore be incorporated into other carrier materials for example plastics, (plastics chains for topical therapy), collagen or bone cement.

The tablets, dragees, capsules, pills and granules may be provided with the conventional coatings and casings optionally comprising opaquing agents and may also be put together so that they release the active ingredient or active ingredients only or preferably in a specific part of the intestinal optionally with sustain release, wherein polymer substances and waxes for example may be used as embedding compounds.

The active ingredients may optionally also be present in microencapsulated form with one or more of the above mentioned excipients.

In addition to the active ingredients suppositories may also contain the conventional water soluble or water insoluble excipients, for example polyethylene glycols, fats, for example cacoa fat and higher esters (for example C_{14}- alcohol with C_{16}-fatty acid) or mixtures of these substances.

In addition to the active ingredients ointments, pastes, creams and gels may contain the conventional excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivative, polyethylene glycols, silicones, bentonites, silicic acid, Talc and zink oxide or mixtures of these substances.

In addition to the active ingredients powders and sprays may contain the conventional excipients, for example lactose, talcum, silicic acid, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays may additionally contain the conventional blowing agents, for example chlorofluorohydrocarbons.

In addition to the active ingredients solutions and emulsions may contain the conventional excipients such as solvents, solubilisers and emulgators, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular cotton seed oil, peanut oil, corn oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances.

The solutions and emulsions may also be present in sterile and blood isotonic form for parenteral application.

In addition to the active ingredients suspensions may contain conventional excipients such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures of these substances.

The active ingredient or the active ingredients of the formulae (I) to (XIV) shall be present in the above mentioned pharmaceutical preparations, preferably in a concentration of approximately 0.1 to 99,5 weight %, preferably of approximately 0.5 to 95 weight % of the total mixture. The ratio of the substances to be individually combined is dependent on the individual active ingredient. Therefore, active agents are present, which are administered in a general dose of 0.1 mg/kg body weight per day (ibandronate and alendronate), 0.5 mg/kg body weight per day (mevastatin, simvastatin, pravastatin, fluvastatin), 10 mg/kg body weight per day (pamidronate).

In addition to the compounds of the formulae (I) to (XIV) and the inhibitors of lipid metabolism the above mentioned pharmaceutical preparations may also contain further pharmaceutical active ingredients, such as antiviral, antiparasitic, antimycotic or antibacterial active agents.

The lipid metabolism inhibitors used according to the invention further may contain sulfonamide, sulfadoxin, artemisinin, atovaquon, chinin, chloroquine, hydroxychloroquin, mefloquin, halofantrin, pyrimethamine, armesin, tetracycline, doxycyclin, proguanil, metronidazol, praziquantil, niclosamide, mebendazol, pyrantel, tiabendazole, diethylcarbazin, piperazin, pyrivinum, metrifonate, oxamniquin, bithionol or suramin or several of these substances.

Preferably lovastatin, atorvastatin, simvastatin, mevastatin, pravastatin and fluvastatin are administered orally, wherein pravastatin and fluvastatin are administered in active form.

In general it has proved advantageous both in human and veterinary medicine to administer the active ingredient or ingredients of formulae (I) and (V) in total quantities of approximately 0.5 to approximately 600, preferably 1 to 200 mg/kg body weight per 24 hours, optionally in the form of several individual doses in order to achieve the desired results. An individual dose contains the active ingredient or ingredients preferably in quantities of approximately 0.5 to approximately 200, in particular 1 to 60 mg/kg body weight. It may, however, be necessary to deviate from the above-mentioned dosages and this is dependent on the nature and the body weight of the patient to be treated, the nature and the severity of the disease, the nature and the method and the application of the pharmaceutical compositions as well as the time scale or interval within the administration takes place.

It has proved advantageous to administer the inhibitors of the lipid metabolism in the known range of dosage, which are known from the treatment of disorders of the lipid metabolism and the calcium and phosphate metabolism. These are total quantities of approximately 0.005 to approximately 200, preferably 0.01 to 100 mg/kg body weight per 24 hours, are optionally administered in the form of several individual doses in order to achieve the desired results. An individual dose contains the active ingredient or ingredients (inhibitors of the lipid metabolism) preferably in quantities of approximately 0.002 to approximately 50, in particular 0.01 to 10 mg/kg body weight. It may however be necessary to deviate from the above-mentioned dosages and this is dependent on the nature and the body weight of the patient to be treated, the nature and the severity of the disease, the nature and the method and the application of the pharmaceutical compositions as well as the time scale or interval within the administration takes place. With amino bisphosphonates it has to be considered that their resorbility is very low. This characteristic is advantageous in the case of an attack in the intestinal tract (for example in the case of amoebic dysentery). Here doses of up to 10 mg/kg body weight pamidronate are administered orally. For injection in general doses up to 2 mg/kg body weight are sufficient.

Thus in some cases it may be sufficient to get by with less than the above mentioned quantity of active ingredient, whilst in other cases the above-stated quantity of active ingredient must be exceeded. The person skilled in the art may determine the optimum dosage and method of application of the active ingredient in each case by virtue of his expert experience.

The lipid metabolism inhibitors according to the invention may be administered in animals in the conventional concentrations and preparations together with the feed or feed preparations or the drinking water.

The lipid metabolism inhibitors may be administered simultaneously, separately or successively.

Example

Preparation anti-infectiously active agents

Preparation for injection

(1) The necessary quantity of the sterile anti-infectiously active agents, 500 mg 3-(N-acetyl-N-hydroxy amino)-propyl-phosphonic acid monosodium salt and 90 mg 3-amino-1-hydroxy-propyliden-1,1-bisphosphonic acid disodium salt are distributed on flasks or ampules. The flasks are sealed hermetically for excluding bacteria. For injection it is taken in 500 ml physiologic solution of sodium chloride respectively and administered.

In principle in the same manner as describe above under (1) further injectable preparations of the anti-infectiously active agents are prepared:

(2) 250 mg 3-(N-formyl-N-hydroxy amino)-propylphosphonic acid -monosodium salt and 1 mg 3-methylpentylamino-1-hydroxypropyliden-1,1-bisphosphonic acid disodium salt are used for injections.

(3) 250 mg 3-(N-formyl-N-hydroxy amino)-trans-1-propenylphosphonic acid - monosodium salt and 90 mg 3-amino-1-hydroxypropyliden-1,1-bisphosphonic acid disodium salt are used as an active ingredient for injection.

Preparation of tablets:
A suitable tablet formulation is formed by the following mixture:

3-(N-formyl-N-hydroxy amino)-propylphosphonic acid -monosodium salt	200 mg
lovastatin	10 mg
mannitol	400 mg
starch	50 mg
magnesium stearate	10 mg

Preparation of capsules

3-(N-formyl-N-hydroxy amino)-propylphosphonic acid monopotassium salt	300 mg
simvastatin	10 mg
magnesium stearate	15 mg

The present ingredients are mixed and then filled into a hard gelatine capsule in usual manner.